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(54) Title: POLYPEPTIDES OF G-COUPLED RECEPTOR PROTEINS, AND COMPOSITIONS AND METHODS THEREOF

(57) Abstract

Compounds, compositions and methods involving purified, isolated and/or synthetic G-protein coupled receptor (GPR) polypeptides that comprise fragments, derivatives and/or consensus peptides of transmembrane domains of G-coupled receptor proteins, wherein the GPR polypeptide has biological activity selected from binding of a GPR ligand to a GPR or modulating the binding of GPR a ligand to a GPR.

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POLYPEPTIDES OF G-COUPLED RECEPTOR PROTEINS, AND COMPOSITIONS AND METHODS THEREOF

FIELD OF THE INVENTION

The present invention relates to compounds, compositions and methods involving synthetic, isolated and/or recombinant G-protein coupled receptor polypeptides that comprise fragments and/or consensus peptides of G-protein coupled receptors.

BACKGROUND OF THE INVENTION

The membrane protein gene superfamily of G-protein coupled receptors (GPRs) has been characterized as having seven putative transmembrane domains. The domains are believed to represent transmembrane α-helices connected by extracellular or cytoplasmic loops. Of the 74 sequenced members of this G-protein receptor superfamily, the shortest sequence of 324 amino acids represents the rat *mas* oncogene and the longest, of 744 amino acids, represents the human thyroid-stimulating hormone (TSH) receptor. GPRs thus include a wide range of biologically active receptors, such as hormone-, viral-, growth factor- and neuroreceptors.

G-protein coupled receptors have been characterized as including these seven conserved hydrophobic stretches of about 20-30 amino acids, connecting at least 8 divergent hydrophilic loops. The G-protein family of coupled receptors includes dopamine receptors which bind in a noncovalent but high affinity manner to neuroleptic drugs used for treating psychotic and neurological disorders. For example, the dopamine D_2 receptor includes these transmembrane domains, two of which (TM III and TM V; see below) have been implicated by site-selective mutagenesis to demonstrate functional, association with D_2 ligands.

Transmembrane domains of G-protein coupled receptors are designated TM1, TM2, TM3, TM4, TM5, TM6 and TM7. TM4, TM5, TM6 and TM7 are the most highly conserved and are postulated to

provide sequences which impart biological activity to GPRs. Most GPRs have single conserved cysteine residues in each of the first two extracellular loops which form disulfide bonds that are believed to stabilize functional protein structure. TM3 is also implicated in signal transduction.

Phosphorylation and lipidation (palmitylation or farnesylation) of cysteine residues can influence signal transduction of some GPRs. Most GPRs contain potential phosphorylation sites (e.g., serine or theronine residues) within the third cytoplasmic loop and/or the carboxy terminus. For several GPRs, such as the β-adrenoreceptor, phosphorylation by protein kinase A and/or specific receptor kinases mediates receptor desensitization.

Non-limiting examples of GPRs include cAMP receptors, adenosine receptors, β-adrenergic receptors, muscarinic acetylcholine receptors, α-adrenergic receptors, serotonin receptors (5-HT), histamine H2 receptors, thrombin receptors, kinin receptors, follicle stimulating hormone receptors, opsins and rhodopsins, odorant receptors, cytomegalovirus receptor, etc. See e.g., Probst et al *DNA and Cell Biology* 11:1-20(1992), which is entirely incorporated herein by reference.

The ligand binding sites of GPRs are believed to comprise a hydrophilic socket formed by several GPR transmembrane domains, which socket is surrounded by hydrophobic residues of the GPRs. The hydrophilic side of each GPR transmembrane helix is postulated to face inward and form the polar ligand binding site. TM3 has been implicated in several GPRs as having a ligand binding site, such as including the TM3 aspartate residue. Additionally, TM5 serines, a TM6 asparagine and TM6 or TM7 phenylalanines or tyrosines are also implicated in ligand binding.

GPRs can be intracellularly coupled by heterotrimeric G-proteins to various intracellular enzymes, ion channels and transporters. See, e.g., Johnson et al *Endoc. Rev.* 10:317-331(1989) ; and Birnbaumer et al *Biochem. Biophys. Acta* 1031:163-224(1990) which references are incorporated entirely herein by reference. GPR agonist binding catalyzes the exchange

of GTP for GDP on the α-subunit of the G-protein. Different G-protein α-subunits preferentially stimulate particular effectors to modulate various biological functions in a cell. Phosphorylation of cytoplasmic residues of GPRs has been identified as an important mechanism for the regulation of G-protein coupling of some GPRs.

As a non-limiting example of a GPR ligand, dopamine (3,4-dihydroxyphenethylamine) is a critical neurotransmitter in the central nervous system (e.g., in the substantia nigra, midbrain, and hypothalamus). Since the elucidation of the ascending mesolimbic and nigrostriatal pathways, these pathways have been found to be critical in the control of both motor initiation (nigrostriatal) behavior and affective (mesolimbic) behavior. The clinical efficacy of the major neuroleptic antipsychotic medications has been found to correlate with the respective affinities of these agents for the dopamine D_2 receptor in the brain. A dopaminergic role in the symptomatology of the major psychoses has thus been hypothesized, although it is unclear if dopamine alone is etiological, (see, e.g., Davis et al. *Am. J. Psych.* 148:1474-1476 (1991)). Nonetheless, this hypothesis has served as a stimulus for current research in this area.

One model for studying possible interactions of G-protein coupled receptors with their ligands has emerged from site-directed mutagenesis and biochemical analysis of the β-adrenergic receptor, as well as from biophysical analysis of the interaction of retinal with opsin.

According to such a model, the binding of a GPR ligand to a G-protein coupled receptor involves multiple interactions between functional groups on the GPR ligand and residues within the hydrophophilic binding site of the receptor.

While a number of the amino acid residues in the dopamine D_2 receptor have been postulated to participate in D_2 ligand binding, based on results obtained from site-directed mutagenesis studies and photoaffinity labeling studies performed on the β-adrenergic receptor, such studies have failed to specifically determine which residues are actually involved in

binding in the D_2 system. Sibley et al. Soc. Neurosci. Abs. 17:36.10, 324.5, 324.6 (1991).

The clinical use of neuroleptics has provided a means for treating patients suffering from psychotic disorders. Short-term use of neuroleptics is indicated in several types of psychotic disorders, e.g., acute psychotic episodes, regardless of type; exacerbations of schizophrenia; acute manic excitement while deferring use of lithium or awaiting onset of its effects; adjunctive therapy for major depression with prominent psychotic symptoms, or when an antidepressant or ECT alone is not successful; for agitation in delirium, dementia, or severe mental retardation while seeking to identify and treat the primary basis of the problem; in certain chronic, degenerative, or idiopathic neuropsychiatric disorders with dyskinesias, such as Huntington's disease or Gilles de la Tourette's syndrome; or for ballism or hemiballism; childhood psychoses or apparently allied conditions marked by severe agitation or aggressive behavior; miscellaneous medical indications, notably nausea and vomiting, or intractable hiccups.

Additionally, continuous long-term use of neuroleptics is indicated in many psychotic disorders, such as (for more than six months) (i) primary indications such as Schizophrenia, Paranoia[a,b], Childhood psychoses, some degenerative or idiopathic neuropsychiatric disorders (notably, Huntington's disease and Gilles de la Tourette's syndrome); (ii) secondary indications such as extremely unstable manic-depressive or other episodic psychoses (unusual), otherwise unmanageable behavior symptoms in dementia, amentia, or other brain syndromes; and (iii) questionable indications such as chronic characterological disorders with schizoid, "borderline," or neurotic characteristics; substance abuse; or antisocial behavior, recurrent mood disorders. See, e.g., Baldessarini, *Chemotherapy in Psychiatry*, Revised and Enlarged Edition, Harvard University Press, Cambridge, MA, (1985), the contents of which is entirely incorporated herein by reference.

Neuroleptics are also referred to as neuroplegics, psychoplegics, psycholeptics, antipsychotics and major

tranquilizers, but are sometimes distinguished from non-neuroleptic anti-psychotics. Neuroleptics have recently been characterized as an agent that produces sedative or tranquilizing effects, and which also produces motor side effects, such as catalepsy or extrapyramidal symptomatology. Nonlimiting representative examples of neuroleptics include phenothiazine derivatives (e.g., chlorpromazine); thioxanthine derivatives (e.g., thiothixene); butyrophenone derivatives (e.g., haloperidol); dihydroindolone (e.g., molindone); dibenzoxazepine derivatives (e.g., loxapine); and "atypical" neuroleptics (e.g., sulpiride, remoxipiride pimozide and clozapine). See Berstein *Clinical Pharmacology* Littleton, Mass.:PSG Publishing (1978); Usdin et al *Clinical Pharmacology in Psychiatry* New York:Elsevier North-Holland (1981); and Baldessarini, *supra*, (1985); and , which references are herein entirely incorporated by reference.

The term "atypical neuroleptics" has been used to describe antipsychotic neuroleptics that produce few or no extrapyramidal side effects and which do not cause catalepsy in animals (See, e.g., Picket et al, *Arch. Gen. Psychiatry* 49:345 (May 1992). Alternatively, atypical neuroleptics, such as clozapine, have been described as those neuroleptics which have a higher affinity for D_4 and D_1 sites than for D_2 sites (See, e.g., Davis et al *Amer. J. Psych.* 148:1474, 1476 (November 1991).

The long term use of all known anti-psychotics, such as neuroleptics or non-neuroleptic antipsychotics, has resulted in serious side effects, as present in Table I, such as persistent and poorly reversible motoric dysfunctions (e.g., tardive dyskinesia) in a significant number of patients. These side effects are especially prevalent in geriatric populations, and adequate pharmacological treatment of these debilitating motoric dysfunctions is not currently available. This problem has severely limited the long-term, clinical administration of these agents.

TABLE I
Neurological Side Effects of
Neuroleptic-Antipsychotic Drugs

Reaction	Features	Period of maximum risk	Proposed mechanism	Treatment
Acute dystonia	Spasm of muscles of tongue, face, neck, back; may mimic seizures; not hysterical	1-5 days	Dopamine excess? Acetylcholine excess?	Antiparkinsonism agents are diagnostic and curative (i.m. or i.v., then p.o.)
Parkinsonism	Bradykinesia, rigidity, variable tremor, mask-facies, shuffling gait	5-30 days (rarely persists)	Dopamine blockade	Antiparkinsonism agents (p.o); dopamine agonists risky?
Akathisia	Motor restlessness; patient may experience anxiety or agitation	5-60 days (commonly persists)	Unknown	Reduce dose or change drug low doses of propranolol;[a] antiparkinsonism agents or or benzodiazepines may help
Tardive dyskinesia	Oral-facial dyskinesia; choreo-athetosis, sometimes irreversible, rarely progressive	6-24 months (worse on withdrawal)	Dopamine excess?	Prevention best; treatment unsatisfactory; slow spontaneous remission
"Rabbit" syndrome	Perioral tremor (late parkinsonism variant?); usually reversible	Months or years	Unknown	Antiparkinsonism agents; reduce dose of neuroleptic
Malignant syndrome	Catatonia, stupor, fever, unstable pulse and blood pressure; myoglobinemia; can be fatal	Weeks	Unknown	Stop neuroleptic; antiparkinsonism agents usually fail; bromocriptine often helps; dantrolene variable; general supportive care crucial

a. There may be an increased risk of hypotension on interacting high doses of propranolol with some antipsychotic agents; clonidine may also be effective at doses of 0.2-0.8 mg/day, but carries a high risk of hypotension (Zubenko et al., *Psychiatry Res.* 11:143, 1984).

In addition, clozapine, although apparently capable of producing less motor side effects, can cause irreversible, potentially fatal agranulocytosis in a minority of patients administered the drug. Such serious side effects limit the use of

clozapine to patients who are resistant to treatment with other neuroleptics.

Antipsychotics have a variety of significant pharmacological effects, e.g., as presented in the following Tables II and III.

Table II

Comparative Pharmacology of Neuroleptics

Pharmacologic Actions	Alkaloid	Phenothiazine Derivative: Chlorpromazine	Thioxanthene Derivative: Thiothixene	Butyrophenone Derivative: Haloperidol
Antipsychotic		Yes + +	Yes + +	Yes + + + +
Antiemetic		Yes + + +	Not tested	Yes + + +
Hypothermia		Yes +	Yes +	No
Hypotension		Yes + +	Yes + + +	+
Parkinsonism		Yes + +	Yes +	Yes + + + +
Antiadrenergic		Yes + +	Yes + + +	+
Anticholinergic		Yes +	Yes +	Negligible
Antihistaminic		Yes +	Negligible	Negligible
Releases NE, DA		No	No	No
Blocks DA		Yes + +	Yes +	Yes + + + +
Blocks NE		Yes + +	Yes + + +	Yes +
Central sympathetic suppressant		Yes + +	Yes +	Yes + + +

Chlorpromazine, thiothixene, and haloperidol decrease the functional availability of dopamine (DA) and norepinephrine (NE) by blocking the dopamine receptor sites in the basal ganglia and norepinephrine receptor sites in thalamic and hypothalamic areas. Reserpine simply reduces the concentrations of norepinephrine and dopamine in these areas. Both of these actions result in suppression of central sympathetic activity. + → + + + + indicates from very weak to very strong effects.

Table III

Comparative Pharmacology of Antipsychotics

Drug	Extrapyramidal Sedation	Adrenergic Blockage	Reaction
Chlorpromazine	High	Moderate to high	Moderate
Chlorprothixene	High	High	Low to moderate
Haloperidol	Low	Low	High
Molindone	Moderate	Moderate	Moderate to high
Loxapine	High	Low to moderate	High

See Ebadi, PHARMACOLOGY, Little, Brown and Co., Boston, 61-65 (1985); Cattabeni et al *Adv. Biochem. Psychopharmacology* 24:275 (1980). Baldessarini, *supra*, which references are herein incorporated entirely by reference.

However, despite the fact that thousands of neuroleptic- or antipsychotic-type compounds have been synthesized and reported in the literature, such compounds which lack serious side effects and which have sufficient pharmacological activity, have not been disclosed.

Alternative to dopamine receptor GPRs, as presented above, other neuroreceptor GPRs are involved in neurological pathologies, and drugs such as neuroreceptor GPR binding agents, presently used for treating these pathologies, also suffer from similar side effects as those of neuroleptics, as presented above.

Other GPRs are also involved in receptor-related pathologies, such as hormone related GPRs involved in endocrine related pathologies.

Accordingly, there is a need to provide G-protein coupled receptor binding agents, including neuroreceptor and endocrine receptor GPRs, which do not produce such deleterious and debilitating side effects as those produced by known agents, such as neuroleptics, which can be used for therapy or diagnosis of GPR related pathologies.

Citation of documents herein is not intended as an admission that any of the documents cited herein is pertinent prior art, or an admission that the cited documents are considered material to the patentabilty of the claims of the present application. All statements as to the date or representations as to the contents of these documents are based on the information available to the applicant and does not constitute any admission as to the correctness of the dates or contents of these documents.

SUMMARY OF THE INVENTION

It is therefore an object of the present invention to overcome one or more deficiencies found in the related art.

It is another object of the present invention to provide non-naturally occurring synthetic, isolated and/or recombinant GPR polypeptides which are fragments, consensus fragments and/or sequences having conservative amino acid substitutions, of at least one transmembrane domain of at least one G-protein coupled receptor, which polypeptides have been discovered to have receptor-like functional binding sites of neuroreceptor and endocrine GPRs, such that GPR polypeptides of the present invention may bind GPR ligands, or which may also modulate, quantitatively or qualitatively, GPR ligand binding to GPRs.

It is still another object of the present invention to provide GPR polypeptides and compositions that have only partially helical structures, in contrast to known characterized transmembrane domains of GPRs, such as, but not limited to, GPR transmembrane domains I-VII.

It is yet another object of the present invention to provide synthetic or recombinant GPR polypeptides, conservative substitution derivatives thereof, antibodies, anti-idiotype antibodies, compositions and methods that can be used as potential modulators of G-protein coupled receptor function, by binding to GPR ligands or modulate GPR ligand binding, due to their expected biological properties, which may be used in diagnostic, therapeutic and/or research applications.

It is a further object of the present invention is to provide synthetic, isolated or recombinant polypeptides which are designed to inhibit or mimic various GPRs or fragments thereof, as receptor types and subtypes.

According to one aspect of the present invention, a synthetic or recombinant GPR polypeptide is provided that comprises a GPR amino acid sequence of, e.g., at least 5, 10, 15 or 20 amino acids, substantially corresponding to at least one transmembrane domain, or fragment and/or consensus peptide thereof, of a G-protein coupled receptor, wherein at least 20 amino acids are preferred. In a preferred embodiment, the polypeptide is (a) chemically synthesized and/or (b) obtained from a recombinant host cell or organism which expresses a recombinant nucleic acid encoding a GPR polypeptide, as defined herein.

In another preferred embodiment, the transmembrane domain is selected from at least one of TM1, TM2, TM3, TM4, TM5, TM6 or TM7, corresponding to transmembrane domains I, II, III, IV, V, VI and VII, respectively, of a GPR. In another preferred embodiment, the transmembrane domain is a dopamine receptor transmembrane domain selected from the group consisting of at least one of a D_1, D_2, D_3, D_4 and D_5 dopamine receptor transmembrane domain. The transmembrane domain, e.g., may be selected from at least one of D_2 receptor transmembrane domains III or V. In still another preferred embodiment, the GPR polypeptide amino acid sequence

substantially corresponding to an amino acid sequence contained in at least one of Fig. 2 (SEQ ID NO:2), Fig. 3 (SEQ ID NO:3) or Fig. 5 (SEQ ID NO:5).

In another aspect of the present invention, a GPR composition is provided, comprising a GPR polypeptide, or a pharmaceutically acceptable ester, ether, sulfate, carbonate, malate, glucuronide or salt thereof, the composition further comprising a pharmaceutically acceptable carrier and/or diluent.

In still another aspect of the present invention, a method is provided for treating a subject suffering from a disease state involving a qualitative or quantitative pathological abnormality of a GPR protein or a biological molecule functionally associated therewith. Such biological molecule may be a membrane cytoplasmic protein, lipid, carbohydrate, saccharide, nucleoside or nucleotide mono-, di-, or tri-phosphate, an enzyme, a co-factor, a nucleic acid, a neurotransmitter, an ion, a carrier, a cell receptor, or any combination thereof.

In a preferred embodiment, the GPR protein is a dopamine receptor and the abnormality involves a dopamine related pathology, wherein the method comprises administering an effective dopamine receptor modulating amount of a GPR polypeptide of the present invention. In another preferred embodiment, the transmembrane domain is a D_2 dopamine receptor domain and the disease state is a psychiatric disorder, such as schizophrenia or schiz affective disorder (see American Psychiatric Association, Revised Manual of Diagnostic and Statistical Criteria for Psychiatric Disorders (DSM-III-R), American Psychiatric Assoc. Press, Washington, DC (1989)).

In another preferred embodiment, the GPR composition is administered as a pharmaceutical composition to provide a GPR polypeptide in an amount ranging from about 0.01 μg to 100 mg/kg, and also preferably, about 10 μg to 10 mg/kg. In another preferred embodiment, the administering is by oral, intravenous, intramuscular, parenteral or topical administration, including mucosal administration to the nasal mucosa or the oral mucosa, by aerosol, nebulizer or drop administration as non-limiting examples.

Other objects of the invention will be apparent to skilled practitioners from the following detailed description and examples relating to the present invention.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1 is the amino acid sequence of a control peptide (SEQ ID NO:1), which is hydrophobic in its properties, but does not correspond to a known GPR transmembrane domain.

Fig. 2 represents the amino acid sequence of a GPR transmembrane polypeptide, polypeptide II (SEQ ID NO:2), which corresponds to a portion of the dopamine D_2 receptor transmembrane segment III.

Fig. 3 represents the amino acid sequence of a transmembrane polypeptide, polypeptide III (SEQ ID NO:3), corresponding to a consensus peptide of the dopamine D_2 receptor transmembrane domains I-VII.

Fig. 4 represents the amino acid sequence of a consensus sequence of transmembrane domains that is shortened to be less than the length required to span a lipid bilayer.

Fig. 5 represents a consensus amino acid sequence of transmembrane domain as a consensus peptide between dopamine receptors D_1 and D_2.

Fig. 6 is a representation of a circular dichroism spectrum of a solution of the consensus polypeptide III (SEQ ID NO:3) of Fig. 3.

Fig. 7 is a graphical representation of radioligand binding assay data comparing control polypeptide II (SEQ ID NO:1) of Fig. 1, labeled as "II" and consensus polypeptide I (SEQ ID NO:3) of Fig. 3, labeled as "I".

Fig. 8A-G are a comparison listing of amino acid sequences of transmembrane domains and adjacent amino acid sequences of representative GPRs (SEQ ID NOS:6-79).

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

The present invention relates to G-protein coupled receptor (GPR) polypeptides which can be used to mimic naturally occurring or isolated GPRs, or to modulate the binding of GPR ligands to GPRs, such as inhibition or enhancement of binding. GPR polypeptides of the present invention can include GPR transmembrane domain fragments and/or consensus peptides thereof, of at least 4-10 amino acids in length, and/or corresponding sequences having conservative amino acid substitutions as "substitution peptides", wherein the GPR polypeptide binds a GPR ligand or modulates the binding of a GPR ligand to a GPR in *vitro*, *in vivo* or *in situ*.

GPR polypeptides of the present invention can be synthesized or recombinantly produced, or optionally purified, to provide commercially useful amounts of GPR polypeptides for use in therapeutic, diagnostic or research applications, according to known method steps, see, e.g., Ausubel et al, eds. Current Protocols in Molecular Biology, Wiley Interscience, N.Y., (1987, 1992); and Sambrook et al, Molecular Cloning, A Laboratory Manual, 2nd edition, Vols. 1-3, Cold Spring Harbor Press, (1989), which references are herein entirely incorporated by reference.

Additionally, GPR polypeptides according to the present invention can be used to generate polyclonal and/or monoclonal antibodies, anti-idiotype antibodies thereto, or fragments thereof, which may used for diagnostic and/or therapeutic applications, according to known method steps, see, e.g., Harlow and Lane, Antibodies: A Laboratory Manual, Cold Spring Harbor Press (1988), which is herein entirely incorporated by reference.

GPR polypeptides, anti-GPR antibodies or anti-idiotype antibodies (or fragments thereof) to GPR polypeptides have been unexpectedly discovered to quantitatively or qualitatively modulate G-protein coupled receptors, such that binding of GPR polypeptides or anti-idiotype antibodies (or fragments thereof) to G-protein coupled receptor ligands may be used for diagnostic research or therapeutic applications of the present invention. Such GPR polypeptides, antibodies or anti-idiotype antibodies of the present invention may therefore be used as modulators of

G-protein coupled receptors, such as neuroreceptors or endocrine receptors, as non-limiting examples.

Binding of such GPR polypeptides, (including GPR fragments, consensus peptides, substitution derivatives and anti-idiotype antibody fragments) of the present invention may be used to treat symptoms of, and provide diagnosis and treatment for, pathologies related to GPRs. Such pathologies have been found to correlate with symptoms occurring in neurological, viral or endocrine pathologies. D_2 receptor-related psychotic disorders, including schizophrenia, now treated with neuroleptics, is a non-limiting example thereof.

The use of synthetic or recombinant GPR polypeptides of the present invention can be preferable to the use of known drugs that bind G-protein coupled receptors, such as neuroleptics that bind or inhibit the biological effect of binding to neuroreceptors as a non-limiting example. Such polypeptides are expected to have significantly less side effects than presently used drugs presently used for inhibiting such receptor binding including neuroleptics, as they would structurally mimic naturally occuring GPRs and/or modulate ligand binding. Thus, GPR polypeptides are expected to have reduced side effects attributable to known foreign compound drugs, with less immunogenicity, and reduced potential for motoric side effects (e.g., extrapyramidal symptoms and/or tardive dyskinesia).

The present invention is also related to the production, by chemical synthesis or recombinant DNA technology, of GPR polypeptides, preferably as small as possible while still retaining sufficiently high affinity or interaction with G-protein coupled receptors to modulate, such as to inhibit or to enhance, binding to such receptors by GPR ligands.

GPR polypeptides of the present invention may include 5-10 to 50-150 amino acid fragments, consensus sequences or substitution sequences of GPRs, e.g., as presented in Fig. 8A-G (SEQ ID NOS:6-79) including, but not limited to, multiple dopamine receptors, cAMP receptors, adenosine receptors, β-adrenergic receptors, muscarinic acetylcholine receptors, α-adrenergic receptors, serotonin receptors (5-HT), histamine H2 receptors,

thrombin receptors, kinin receptors, follicle stimulating hormone receptors, opsins and rhodopsins, odorant receptors, cytomegalovirus GPRs, adenosine A2 receptors, dopamine receptor, histamine H2 receptors, octopanmine receptors, N-formyl receptors, anaphylatoxin receptors, thromboxane receptors, IL-8 receptors, platelet activating factor receptors, endothelin receptors, bombesin gastrin releasing peptide receptor, neuromedin B preferring bombesin receptors, vasoactive intestinal peptides, neurotensin receptors, bradykinin receptors, thyrotropin-releasing hormone receptors, substance P receptors, neuromedin K receptors, adrenal angiotensen II type I receptors, *mas* oncogene (angiotensin) receptors lutropin-choriogonadotropin receptors, thyrotropin receptors, follicle stimulating hormone receptors, cannabinoid receptors, glucocorticoid-induced receptors, endothelial cell GPRs, testis GPRs, and thoracic aorta GPRs, and homologs thereof having a homology of at least 80% with at least one of transmembrane domains 1-7, as described herein. See, e.g., Probst et al *DNA and Cell Biology* 11:1-20(1992), which is entirely incorporated herein by reference.

Accordingly, a "G-protein coupled receptor polypeptide" or "GPR polypeptide" of the present invention includes polypeptides having a "GPR amino acid sequence" which substantially corresponds to at least one 10 to 50 amino acid fragment and/or consensus sequence of a known GPR or group of GPRs, wherein the GPR polypeptide has homology of at least 80%, such as 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99 or 100% homology, while maintaining GPR modulating activity, wherein a GPR polypeptide of the present invention is not naturally occurring or is naturally occurring but is in a purified or isolated form <u>which does not</u> occur in nature. Preferably, a GPR polypeptide of the present invention substantially corresponds to a transmembrane domain of a GPR or group of GPRs as a consensus sequence.

Also preferred are GPR polypeptides wherein the GPR amino acid sequence is 4-10 to 50 amino acids in length, such as 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39,

40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 60, 70, 80, 90, 100, 110, 120, 130, 140 or 150 amino acids, or any range therein.

An amino acid or nucleic acid sequence of a GPR polypeptide of the present invention is said to "substantially correspond" to another amino acid or nucleic acid sequence, respectively, if the sequence of amino acids or nucleic acid in both molecules provides polypeptides having biological activity that is substantially similar, qualitatively or quantitatively, to the corresponding fragment of at least one GPR transmembrane domain, or which may be synergistic when two or more transmembrane domains, consensus sequences or homologs thereof are present.

Additionally or alternatively, such "substantially corresponding" sequences of GPR polypeptides include conservative amino acid or nucleotide substitutions, or degenerate nucleotide codon substitutions wherein individual amino acid or nucleotide substitutions are well known in the art.

Alternatively or additionally, substantially corresponding refers to GPR polypeptides having amino acid sequences having at least 80% homology or identity to an amino acid sequence of SEQ ID NO:1, such as 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99 or 100% homology or identity.

Accordingly, GPR polypeptides of the present invention, or nucleic acid encoding therefor, include a finite set of substantially corresponding sequences as substitution peptides or polynucleotides which can be routinely obtained by one of ordinary skill in the art, without undue experimentation, based on the teachings and guidance presented herein. For a detailed description of protein chemistry and structure, see Schulz, G.E. et al., *Principles of Protein Structure*, Springer-Verlag, New York, 1978, and Creighton, T.E., *Proteins: Structure and Molecular Properties*, W.H. Freeman & Co., San Francisco, 1983, which are hereby incorporated by reference. For a presentation of nucleotide sequence substitutions, such as codon preferences, see Ausubel et al, *supra*, at §§ A.1.1-A.1.24, and Sambrook et al, *supra*, at Appendices C and D.

Conservative substitutions of a GPR polypeptide of the present invention includes a variant wherein at least one amino acid residue in the polypeptide has been conservatively replaced by a different amino acid. Such substitutions preferably are made in accordance with the following list as presented in Table IV, which substitutions may be determined by routine experimentation to provide modified structural and functional properties of a synthesized polypeptide molecule, while maintaining the receptor binding, inhibiting or mimicking biological activity, as determined by known GPR receptor activity assays.

Table IV

Original Residue	Exemplary Substitution
Ala	Gly;Ser
Arg	Lys
Asn	Gln;His
Asp	Glu
Cys	Ser
Gln	Asn
Glu	Asp
Gly	Ala;Pro
His	Asn;Gln
Ile	Leu;Val
Leu	Ile;Val
Lys	Arg;Gln;Glu
Met	Leu;Tyr;Ile
Phe	Met;Leu;Tyr
Ser	Thr
Thr	Ser
Trp	Tyr
Tyr	Trp;Phe
Val	Ile;Leu

Alternatively, another group of substitutions of GPR polypeptides of the present invention are those in which at least one amino acid residue in the protein molecule has been removed and a different residue inserted in its place according to the following Table V. The types of substitutions which may be made in the protein or peptide molecule of the present invention may be based on analysis of the frequencies of amino acid changes between a homologous protein of different species, such as those presented in Table 1-2 of Schulz et al., supra and Figs. 3-9 of Creighton, supra.

Based on such an analysis, alternative conservative substitutions are defined herein as exchanges within one of the following five groups:

TABLE V

1. Small aliphatic, nonpolar or slightly polar residues: Ala, Ser, Thr (Pro, Gly);
2. Polar, negatively charged residues and their amides: Asp, Asn, Glu, Gln;
3. Polar, positively charged residues: His, Arg, Lys;
4. Large aliphatic, nonpolar residues: Met, Leu, Ile, Val (Cys); and
5. Large aromatic residues: Phe, Tyr, Trp.

The three amino acid residues in parentheses above have special roles in protein architecture. Gly is the only residue lacking any side chain and thus imparts flexibility to the chain. This however tends to promote the formation of secondary structure other than α-helical. Pro, because of its unusual geometry, tightly constrains the chain. It generally tends to promote β-turn-like structures, although in some cases Cys can be capable of participating in disulfide bond formation which is important in protein folding. Note the Schulz et al. would merge Groups 1 and 2, above. Note also that Tyr, because of its hydrogen bonding potential, has significant kinship with Ser, and Thr, etc.

Conservative amino acid substitutions according to the present invention, e.g., as presented above, are known in the art and would be expected to maintain biological and structural properties of the polypeptide after amino acid substitution. Most deletions and insertions, and substitutions according to the present invention are those which do not produce radical changes in the characteristics of the protein or peptide molecule. "Characteristics" is defined in a non-inclusive manner to define both changes in secondary structure, e.g. α-helix or β-sheet, as well as changes in physiological activity, e.g. in receptor binding assays.

However, when the exact effect of the substitution, deletion, or insertion is to be confirmed one skilled in the art will appreciate that the effect of the substitution or substitutions will be evaluated by routine screening assays, either immunoassays or bioassays to confirm biological activity, such as receptor binding or modulation of ligand binding to the corresponding GPR. See, e.g., Maranges et al., eds., for example, a substituted polypeptide

typically is made by site-specific mutagenesis of the peptide molecule-encoding nucleic acid, expression of the mutant nucleic acid in recombinant cell culture, and, optionally, purification from the cell culture, for example, by immunoaffinity chromatography using a specific antibody on a chemically derivatized column or immobilized membranes or hollow fibers (to absorb the mutant by binding to at least one epitope).

A preferred use of this invention is the production, by chemical or recombinant DNA technology, of GPR polypeptides, preferably as small as possible while still retaining sufficiently high affinity for binding to, or association with, GPRs. By production of GPR polypeptides including smaller fragments or variants of such transmembrane domains, one skilled in the art, using known binding and inhibition assays, can readily identify the GPR polypeptides capable of binding minimizing or modulating G-protein coupled receptors using known methods. Non-limiting examples of fragments of GPRs to be used as GPR polypeptides or as a basis for consensus sequences thereof for GPR polypeptides, are presented in Figs. 2-5 and Fig. 8A-G, wherein fragments or consensus sequences of 10 to 50 amino acids of at least one sequence of Figs. 2-5 or corresponding to at least one transmembrane domain or domains 1-7 listed in Fig. 8A-G (SEQ ID NOS:6-79) are encompassed by the present invention, such as at least one transmembrane domain of one or more GPRs, such as a cAMP receptor (1), adenosine receptors (2-3); muscarinic acetylcholine receptors (4-8); human adrenergic receptors (9-11, 14-16, 19-25, 28); adrenergic receptors (9-28); human thrombin receptor (31); endothelin receptors (35-36), bombesin receptors (37-38), endocrine receptors (48-50), rhodopsin (51). opsins (52-54), odorant receptors (55-64), and cytomegalovirus GPRs (72-54), as non-limiting examples, wherein ("#") refers to the listed sequences in Fig. 8A-G.

Accordingly, GPR polypeptides may include consensus sequences and/or fragments of at least one of transmembrane domain 1-7 of one or more GPRs as presented in Figs. 2-5 (SEQ ID NO:2-5) or Fig. 8A-G. (SEQ ID NOS:6-79) or homologs thereof, which GPR polypeptides do not occur naturally, and/or which are provided in an isolated and/or purified form not found in nature.

Consensus peptides of GPR polypeptides of the present invention may include peptides which are distinct from known GPR sequences in critical structural features, but which are derived from consensus sequences of homologous GPR transmembrane domains 1-7, e.g., as presented in Fig. 8A-G (SEQ ID NOS:6-79). Such consensus peptides may be derived by molecular modeling, optionally combined with hydrophobicity analysis and/or fitting to model helices, as non-limiting examples. Such modeling can be accomplished according to known method steps using known modeling algorithms, such as, but not limited to, ECEPP, INSIGHT, DISCOVER, CHEM-DRAW, AMBER, FRODO and CHEM-X. Such algorithms compare transmembrane domains between related G-protein coupled receptors, determine probable energy-miminized structures and define alternative consensus polypeptide fragments.

Such consensus peptides or fragments of GPRs may then be synthesized or produced recombinantly, in order to provide GPR polypeptides according to the present invention which mimic, modulate or inhibit binding of ligands to G-protein coupled receptors. GPR ligands, in the context of the present invention, refer to biological molecules that bind GPRs *in vitro*, *in situ* or *in vivo*, and may include hormones, neurotransmitters, viruses or receptor binding domains, thereof, opsins, rhodopsins, nucleosides, nucleotides, coagulation cascade factors, odorants or pheremones, toxins, colony stimulating factors, platelet activating factors, neuroactive peptides, neurohumors, or any biologically active compounds, such as drugs or synthetic or naturally occurring compounds.

The following non-limiting examples of consensus peptides of GPRs of the present invention are provided by way of guidance and not by way of limitation. In GPR polypeptides of the present invention, one or more, preferably 4-10, Asp and/or Lys residues may additionally be incorporated at the carboxy and/or amino terminal ends in order to provide expected helix forming effects of the helix dipole effect, e.g., as described in Baldwin et al *Biochem.* 28:2130 (1989); Baldwin et al *Proc. Nat'l Acad. Sci. USA* 84:8898 (1987); and Baldwin et al *Proc. Nat'l Acad. Sci. USA* 86:5286 (1989), which references are entirely incorporated herein by reference.

As a non-limiting example of GPR polypeptide of the present invention, dopamine receptor transmembrane fragments of D_2 transmembrane domain (e.g., domain III) as presented in Fig. 2 (SEQ ID NO:2) or a consensus sequence as presented in Fig. 3 (SEQ ID NO:3), e.g., of D_2 domains I-VII. Additionally or alternatively a consensus sequence may include less than 20 amino acids, such as 15 amino acids corresponding to a transmembrane domain, such as a D_2 receptor domain, as presented in Fig. 4 (SEQ ID NO:4) as polypeptide IV, which is smaller than the length required by spanning an average lipid bilayer of a cell membrane.

However, in the context of the present invention, GPR polypeptides of greater than 15 -20 amino acids are preferred such that the GPR polypeptides are able to span the lipid bilayer.

Another non-limiting example of a GPR polypeptide using dopamine receptor transmembrane domains is a consensus sequence of two or more GPR receptors, such as the dopamine D_1 and D_2 receptors. A non-limiting example of such a consensus GPR polypeptide is presented in Fig. 5 (SEQ ID NO:5).

Additionally, modified amino acids or chemical derivatives of amino acids of consensus or fragments of GPRs proteins, according to the present invention may be provided, which polypeptides contain additional chemical moieties or modified amino acids not normally a part of the protein. Covalent modifications of the peptide are thus included within the scope of the present invention. Such modifications may be introduced into a GPR polypeptide by reacting targeted amino acid residues of the polypeptide with an organic derivatizing agent that is capable of reacting with selected side chains or terminal residues. The following examples of chemical derivatives are provided by way of illustration and not by way of limitation.

Aromatic amino acids may be replaced with D- or L-naphylalanine, D- or L-Phenylglycine, D- or L-2-thieneylalanine, D- or L-1-, 2-, 3- or 4-pyreneylalanine, D- or L-3-thieneylalanine, D- or L-(2-pyridinyl)-alanine, D- or L-(3-pyridinyl)-alanine, D- or L-(2-pyrazinyl)-alanine, D- or L-(4-isopropyl)-phenylglycine, D-(trifluoromethyl)-phenylglycine, D-(trifluoromethyl)-phenylalanine, D-p-fluorophenylalanine, D- or L-p-biphenylphenylalanine, D- or

L-p-methoxybiphenylphenylalanine, D- or L-2-indole(alkyl)alanines, and D- or L-alkylainines where alkyl may be substituted or unsubstituted methyl, ethyl, propyl, hexyl, butyl, pentyl, iso-propyl, iso-butyl, sec-isotyl, iso-pentyl, non-acidic amino acids, of C1-C20.

Acidic amino acids can be substituted with non-carboxylate amino acids while maintaining a negative charge, and derivatives or analogs thereof, such as the non-limiting examples of (phosphono)-alanine, glycine, leucine, isoleucine, threonine, or serine; or sulfated (e.g., -SO_3H) threonine, serine, tyrosine.

Other substitutions may include unnatural hyroxylated amino acids may made by combining "alkyl" (as defined and exemplified herein) with any natural amino acid. Basic amino acids may be substituted with alkyl groups at any position of the naturally occurring amino acids lysine, arginine, ornithine, citrulline, or (guanidino)-acetic acid, or other (guanidino)alkyl-acetic acids, where "alkyl" is define as above. Nitrile derivatives (e.g., containing the CN-moiety in place of COOH) may also be substituted for asparagine or glutamine, and methionine sulfoxide may be substituted for methionine. Methods of preparation of such peptide derivatives are well known to one skilled in the art.

In addition, any amide linkage in any of the GPR polypeptides can be replaced by a ketomethylene moiety, e.g. (-C(=O)-CH_2-) for (-(C=O)-NH-). Such derivatives are expected to have the property of increased stability to degradation by enzymes, and therefore possess advantages for the formulation of compounds which may have increased *in vivo* half lives, as administered by oral, intravenous, intramuscular, intraperitoneal, topical, rectal, intraocular, or other routes.

In addition, any amino acid representing a component of the said peptides can be replaced by the same amino acid but of the opposite chirality. Thus, any amino acid naturally occurring in the L-configuration (which may also be referred to as the R or S, depending upon the structure of the chemical entity) may be replaced with an amino acid of the same chemical structural type, but of the opposite chirality, generally referred to as the D- amino acid but which can additionally be referred to as the R- or the S-, depending

upon its composition and chemical configuration. Such derivatives have the property of greatly increased stability to degradation by enzymes, and therefore are advantageous in the formulation of compounds which may have longer *in vivo* half lives, when administered by oral, intravenous, intramuscular, intraperitoneal, topical, rectal, intraocular, or other routes.

Additional amino acid modifications of amino acids of GPR polypeptides of to the present invention may include the following: Cysteinyl residues may be reacted with alpha-haloacetates (and corresponding amines), such as 2-chloroacetic acid or chloroacetamide, to give carboxymethyl or carboxyamidomethyl derivatives. Cysteinyl residues may also be derivatized by reaction with compounds such as bromotrifluoroacetone, alpha-bromo-beta-(5-imidozoyl)propionic acid, chloroacetyl phosphate, N-alkylmaleimides, 3-nitro-2-pyridyl disulfide, methyl 2-pyridyl disulfide, p-chloromercuribenzoate, 2-chloromercuri-4-nitrophenol, or chloro-7-nitrobenzo-2-oxa-1,3-diazole.

Histidyl residues may be derivatized by reaction with compounds such as diethylprocarbonate e.g., at pH 5.5-7.0 because this agent is relatively specific for the histidyl side chain, and para-bromophenacyl bromide may also be used; e.g., where the reaction is preferably performed in 0.1 M sodium cacodylate at pH 6.0.

Lysinyl and amino terminal residues may be reacted with compounds such as succinic or other carboxylic acid anhydrides. Derivatization with these agents is expected to have the effect of reversing the charge of the lysinyl residues. Other suitable reagents for derivatizing alpha-amino-containing residues include compounds such as imidoesters/e.g., as methyl picolinimidate; pyridoxal phosphate; pyridoxal; chloroborohydride; trinitrobenzenesulfonic acid; O-methylisourea; 2,4 pentanedione; and transaminase-catalyzed reaction with glyoxylate.

Arginyl residues may be modified by reaction with one or several conventional reagents, among them phenylglyoxal, 2,3-butanedione, 1,2-cyclohexanedione, and ninhydrin according to known method steps. Derivatization of arginine residues requires that the reaction be performed in alkaline conditions because of the high pKa of the guanidine functional group. Furthermore, these

reagents may react with the groups of lysine as well as the arginine epsilon-amino group.

The specific modification of tyrosyl residues per se is well-known, such as for introducing spectral labels into tyrosyl residues by reaction with aromatic diazonium compounds or tetranitromethane. N-acetylimidizol and tetranitromethane may be used to form O-acetyl tyrosyl species and 3-nitro derivatives, respectively.

Carboxyl side groups (aspartyl or glutamyl) may be selectively modified by reaction with carbodiimides (R' N-C-N-R') such as 1-cyclohexyl-3-(2-morpholinyl- (4-ethyl) carbodiimide or 1-ethyl-3-(4-azonia-4,4- dimethylpentyl) carbodiimide. Furthermore, aspartyl and glutamyl residues may be converted to asparaginyl and glutaminyl residues by reaction with ammonium ions.

Glutaminyl and asparaginyl residues may be frequently deamidated to the corresponding glutamyl and aspartyl residues. Alternatively, these residues may be deamidated under mildly acidic conditions. Either form of these residues falls within the scope of the present invention.

Derivatization with bifunctional agents is useful for cross-linking the peptide to a water-insoluble support matrix or to other macromolecular carriers, according to known method steps. Commonly used cross-linking agents include, e.g., 1,1-bis(diazoacetyl)-2-phenylethane, glutaraldehyde, N-hydroxysuccinimide esters, for example, esters with 4-azidosalicylic acid, homobifunctional imidoesters, including disuccinimidyl esters such as 3,3'-dithiobis(succinimidylpropionate), and bifunctional maleimides such as bis-N-maleimido-1,8-octane. Derivatizing agents such as methyl-3-[(p-azidophenyl)dithio]propioimidate yield photoactivatable intermediates that are capable of forming crosslinks in the presence of light. Alternatively, reactive water-insoluble matrices such as cyanogen bromide-activated carbohydrates and the reactive substrates described in U.S. Patent Nos. 3,969,287; 3,691,016; 4,195,128; 4,247,642; 4,229,537; and 4,330,440 (which are herein incorporated entirely by reference), may be employed for protein immobilization.

Other modifications of GPR polypeptides of the present invention may include hydroxylation of proline and lysine, phosphorylation of hydroxyl groups of seryl or threonyl residues, methylation of the alpha-amino groups of lysine, arginine, and histidine side chains (T.E. Creighton, *Proteins: Structure and Molecule Properties*, W.H. Freeman & Co., San Francisco, pp. 79-86 (1983)), acetylation of the N-terminal amine, methylation of main chain amide residues (or substitution with N-methyl amino acids) and, in some instances, amidation of the C-terminal carboxyl groups, according to known method steps.

Such derivatized moieties may improve the solubility, absorption, permeability across the blood brain barrier biological half life, and the like. Such moieties or modifications of GPR polypeptides may alternatively eliminate or attenuate any possible undesirable side effect of the protein and the like. Moieties capable of mediating such effects are disclosed for example, in *Remington's Pharmaceutical Sciences*, 16th ed., Mack Publishing Co., Easton, PA (1980).

Such chemical derivatives of GPR polypeptides also may provide attachment to solid supports, including but not limited to, agarose, cellulose, hollow fibers, or other polymeric carbohydrates such as agarose, cellulose, such as for purification, generation of antibodies or cloning; or to provide altered physical properties, such as resistance to enzymatic degradation or increased binding affinity or modulation for GPRs, which is desired for therapeutic compositions comprising GPR polypeptides, antibodies thereto or fragments thereof. Such peptide derivatives are well-known in the art, as well as method steps for making such derivatives using carbodiimides active esters of N-hydroxy succinimmide, or mixed anhydrides, as non-limiting examples.

Variation upon consensus peptide sequences of GPR polypeptide of the present invention may also include: the addition of one, two, three, four, or five lysine, arginine or other basic residues added to the -COOH terminal end of the peptide; and/or one, two, three, four, or five glutamate or aspartate or other acidic residues added to the amino terminal end of the peptide, where "acidic" and "basic" are as defined herein. Such modifications are

well known to increase the α-helical content of the peptide by the "helix dipole effect". They also can provide enhanced aqueous solubility of the peptide. See, e.g., Baldwin et al., supra

As another non-limiting example of a GPR polypeptide of the present invention, serotonergic receptors (5-HT) consensus sequences may be determined using presently known 5-HT sequences and include, e.g., as consensus peptides of TM3, TM5 and TM7, respectively:

5-HT consensus (1) DDDDNIWSIFDWIGYLNSISMVIYTLFKKKK (SEQ ID NO:80)
5-HT consensus (2) DDDDNIWNIFSTIGYLNSISPVSVIMHIYGKKKK (SEQ ID NO:81)
5-HT consensus (3) DDDDGYSIYDTLVTFAINPVYITVFKKKK (SEQ ID NO:82)

Such non-naturally occurring consensus sequences may also be further modified according to known method steps to provide additional consensus peptides with substituted amino acids to increase or decrease α-helical propensity and/or solubility (e.g., hydrophilicity). As a non-limiting example, 5-HT consensus peptide (1) above may be modified according to the present invention to have increase helical propensity and increased aqueous solubility as follows:

5-HT consensus (4) DDDDNAWSAFDWALYLNSISMAIYTYAKKKK (SEQ ID NO:83),

wherein, e.g., smaller, non-polar residues replace either larger, more polar residues (e.g., Ala for Ile or Val) or larger aromatic residues (e.g., Ala for Phe).

Another non-limiting, illustrative example of consensus GPR polypeptides of the present invention are those for adrenergic receptors, are the following:

An example of the consensus GPR polypeptide for domain VII across all presently known adrenergic receptors is as follows:

adrenergic consensus(1) LFSFITWLGYANSSLNPIIYTTF (SEQ ID NO:84)

An example of a consensus GPR polypeptide for domain V across all adrenergic receptors is as follows:

adrenergic consensus(2) VYTIYSSSVVFFAPSLAIMVITYT (SEQ ID NO:85)

Examples of a consensus GPR polypeptide for domain III across all adrenergic receptors are as follows:

adrenergic consensus(3) IWLTSDIMSTSSILHNLCVISF (SEQ ID NO:86)

An example of a consensus GPR polypeptide for domains III, V, and VII of all adrenergic receptors is as follows:

adrenergic consensus(4) IWSIFSSDIVVGYANHSSLAIMCPIVIYTV (SEQ ID NO:87)

adrenergic consensus(5) IFTIFSSDIAVGYANHSSAAIMPIVIYSV (SEQ ID NO:88),

Wherein variations and substitutions of amino acids may be made as described herein.

Non-limiting examples of consensus GPR polypeptides for transmembrane domain III across several or many, such as 1-500, or any range or value therein, G-protein receptors are as follows:

TM3-(1) YAIFVLYASAWLSFLNCPFIVTLNI (SEQ ID NO:96)
TM3-(2) YAIFVLYATAWLSFLNCPFIVTLNI(SEQ ID NO:97)
TM3-(3) YAIFVLYATAWLTFLNCPFIVTLNI(SEQ ID NO:98)
TM3-(4) YAIFVLYASAWLTFLNCPFIVTLNI(SEQ ID NO:99)
TM3-(5) WAIFVLYASAWLSFLNCPFIVTLNI(SEQ ID NO:100)
TM3-(6) WAIFVLYATAWLSFLNCPFIVTLNI(SEQ ID NO:101)
TM3-(7) WAIFVLYATAWLTFLNCPFIVTLNI(SEQ ID NO:102)
TM3-(8) WAIFVLYASAWLTFLNCPFIVTLNI(SEQ ID NO:103)
TM3-(9) YAVFVLYASAWLSFLNMPFIVTLNI(SEQ ID NO:104)
TM3-(10) YAVFVLYATAWLSFLNMPFIVTLNI(SEQ ID NO:105)
TM3-(11) YAVFVLYATAWLTFLNMPFIVTLNI(SEQ ID NO:106)
TM3-(12) YAVFVLYASAWLTFLNMPFIVTLNI(SEQ ID NO:107)
TM3-(13) YAIFVLYASAWLSFLNCVTASIPFIVTLNI(SEQ ID NO:108)
TM3-(14) YAIFVLYASAWLSFLNCTSSIVVTASIVTLNI(SEQ ID NO:109)
TM3-(15) YAIFVLYASAWLSFLNVTLNICTSSIV(SEQ ID NO:110)
TM3-(16) YAIFVLYASAWLSFLNTASILNLMFIVTLNI(SEQ ID NO:111)
TM3-(17) YAIFVLYASAWLSFLNMASILNLPFIVTLNI(SEQ ID NO:112)
TM3-(18) YAIFVLYASAWLSFLNSGILLLAPFIVTLNI(SEQ ID NO:113)
TM3-(19) YAIFVLYASAWLSFLNMSGILLLAPFIVTLNI(SEQ ID NO:114)
TM3-(20) YAIFVLYASAWLSFLNSELSVYTLTVCPFIVTLNI(SEQ ID NO:115)
TM3-(21) YAIFVLYASAWLSFLNMSELSVYTLTVPFIVTLNI(SEQ ID NO:116)

TM3-(22) YAIFVLYASAWLASELSVYTLTVSFLNCPFIVTLNI(SEQ ID NO:117)
TM3-(23) YAIFVLYASAWLASELSVYTLTVPFIVTLNI(SEQ ID NO:118)
TM3-(24) YAIFVLYASAWLSFLASELSVYASELSSTLTTVNMPFIVTLNI(SEQ ID NO:119)
TM3-(25) YAIFVLYASAWLSFLNGGEIALWSLCPFIVTLNI(SEQ ID NO:120)
TM3-(26) YAIFVLYASAWLSFLNGGEIALWSLIVTLNI(SEQ ID NO:121)
TM3-(27) YAIFVLYASAWLGGEIALWSLNCPFIVTLNI(SEQ ID NO:122)
TM3-(28) YAIFVLYAGGEIALWSLSFLNCPFIVTLNI(SEQ ID NO:123)
TM3-(29) YAIFVLYASAWLSFFFLLFGYLGNFLLNCPFIVTLNI(SEQ ID NO:124)
TM3-(30) YAIFVLYASAWLFFFLLFGYLGNFLLPFIVTLNI(SEQ ID NO:125)
TM3-(31) YAIFVLYASAWLSFLNTACFYVAITASLCFITEIALIPFIVTLNI(SEQ ID NO:126)
TM3-(32) YAIFVLYASAWLTACFYVAITASLCFITEIALICPFIVTLNI(SEQ ID NO:127)
TM3-(33) YAIFVLYATACFYVAITASLCFITEIALISFLNCPFIVTLNI(SEQ ID NO:128)
TM3-(34) YAITACFYVAITASLCFITEIALIASAWLSFLNCPFIVTLNI(SEQ ID NO:129)
TM3-(35) YAIFVLYATACFYVAIITEIALISAWLSFLNCPFIVTLNI(SEQ ID NO:130)
TM3-(36) YAIFVLYASAWLSFLNACFYICLFAGVCFLIPFIVTLNI(SEQ ID NO:131)
TM3-(37) YAIFVLYASAWNACFYICLFAGVMFLILSFLNCPFIVTLNI(SEQ ID NO:132)
TM3-(38) YAIFVLYFYICLFAGVCFLIASAWLSFLNCPFIVTLNI(SEQ ID NO:133)
TM3-(39) YAIFVLYASVDAVNMFTSAWLSFLNCPFIVTLNI(SEQ ID NO:134)
TM3-(40) YAIFSVDAVNMFTVLYASAWLSFLNCPFIVTLNI(SEQ ID NO:135)
TM3-(41) YAIFVLYASAWLSVDAVNMFTSFLNCPFIVTLNI(SEQ ID NO:136)
TM3-(42) YAIFVLYASAWLSFLNSVDAVNMFTPFIVTLNI(SEQ ID NO:137)
TM3-(43) YAIFVLYASAWLSFLNCPFIVSVDAVNMFTTLNI(SEQ ID NO:138)
TM3-(44) YAIFVLYASAWLSVDMFTSFLNCPFIVTLNI(SEQ ID NO:139)
TM3-(45) YAISVDAVNMFTFVLYASAWLSFLNCPFIVTLNI(SEQ ID NO:140)
TM3-(46) YAIFSLSVFSLLAIVLYASAWLSFLNCPFIVTLNI(SEQ ID NO:141)
TM3-(47) YAIFVLYASLSVFSLLAISAWLSFLNCPFIVTLNI(SEQ ID NO:142)
TM3-(48) YAIFVLYASAWLSLSVFSLLAISFLNCPFIVTLNI(SEQ ID NO:143)
TM3-(49) YAIFVLYASAWLSFLSLSVFSLLAINCPFIVTLNI(SEQ ID NO:144)
TM3-(50) YAIFVLYASAWLSFLNPFSLSVFSLLAIIVTLNI(SEQ ID NO:145)
TM3-(51) YAIFVLYATAWLTFLNCVTATIPFIVTLNI(SEQ ID NO:146)
TM3-(52) YAIFVLYATAWLSFLNCTSSIVVTATIVTLNI(SEQ ID NO:147)
TM3-(53) YAIFVLYATAWLSFLNVTLNICTTTIV(SEQ ID NO:148)
TM3-(54) YAIFVLYATAWLTFLNTATILNLMFIVTLNI(SEQ ID NO:149)
TM3-(55) YAIFVLYATAWLSFLNMATILNLPFIVTLNI(SEQ ID NO:150)
TM3-(56) YAIFVLYATAWLTFLNSGILLLAPFIVTLNI(SEQ ID NO:151)
TM3-(57) YAIFVLYASAWLTFLNMTGILLLAPFIVTLNI(SEQ ID NO:152)
TM3-(58) YAIFVLYASAWLTFLNTELTVYTLTVCPFIVTLNI(SEQ ID NO:153)
TM3-(59) YAIFVLYASAWLTFLNMTELTVYTLTVPFIVTLNI(SEQ ID NO:154)
TM3-(60) YAIFVLYATAWLATELTVYTLTVTFLNCPFIVTLNI(SEQ ID NO:155)
TM3-(61) YAIFVLYASAWLATELSVYTLTVPFIVTLNI(SEQ ID NO:156)
TM3-(62) YAIFVLYATAWLSFLATELSVYASELSTTLTTVNMPFIVTLNI(SEQ ID NO:157)
TM3-(63) YAIFVLYATAWLSFLNGGEIALWTLCPFIVTLNI(SEQ ID NO:158)
TM3-(64) YAIFVLYASAWLTFLNGGEIALWTLIVTLNI(SEQ ID NO:159)
TM3-(65) YAIFVLYASAWLGGEIALWTLNCPFIVTLNI(SEQ ID NO:160)
TM3-(66) YAIFVLYAGGEIALWTLSFLNCPFIVTLNI(SEQ ID NO:161)

TM3-(67) YAIFVLYATAWLSFFFLLFGYLGNFLLNCPFIVTLNI(SEQ ID NO:162)
TM3-(68) YAIFVLYATAWLFFFLLFGYLGNFLLPFIVTLNI(SEQ ID NO:163)
TM3-(69) YAIFVLYATAWLTFLNTACFYVAITASLCFITEIALIPFIVTLNI(SEQ ID NO:164)
TM3-(70) YAIFVLYATAWLTACFYVAITATLCFITEIALICPFIVTLNI(SEQ ID NO:165)
TM3-(71) YAIFVLYATACFYVAITATLCFITEIALISFLNCPFIVTLNI(SEQ ID NO:166)
TM3-(72) YAITACFYVAITASLCFITEIALIATAWLTFLNCPFIVTLNI(SEQ ID NO:167)
TM3-(73) YAIFVLYATACFYVAIITEIALITAWLTFLNCPFIVTLNI(SEQ ID NO:168)
TM3-(74) YAIFVLYASAWLTFLNACFYICLFAGVCFLIPFIVTLNI(SEQ ID NO:169)
TM3-(75) YAIFVLYASAWNACFYICLFAGVMFLILTFLNCPFIVTLNI(SEQ ID NO:170)
TM3-(76) YAIFVLYFYICLFAGVCFLIATAWLTFLNCPFIVTLNI(SEQ ID NO:171)
TM3-(77) YAIFVLYATVDAVNMFTTAWLTFLNCPFIVTLNI(SEQ ID NO:172)
TM3-(78) YAIFTVDAVNMFTVLYATAWLTFLNCPFIVTLNI(SEQ ID NO:173)
TM3-(79) YAIFVLYATAWLTVDAVNMFTSFLNCPFIVTLNI(SEQ ID NO:174)
TM3-(80) YAIFVLYATAWLSFLNTVDAVNMFTPFIVTLNI(SEQ ID NO:175)
TM3-(81) YAIFVLYASAWLTFLNCPFIVSVDAVNMFTTLNI(SEQ ID NO:176)
TM3-(82) YAIFVLYATAWLSVDMFTTFLNCPFIVTLNI(SEQ ID NO:177)
TM3-(83) YAISVDAVNMFTFVLYATAWLSFLNCPFIVTLNI(SEQ ID NO:178)
TM3-(84) YAIFVLYASLTVFSLLAISAWLTFLNCPFIVTLNI(SEQ ID NO:179)
TM3-(85) YAIFVLYASAWLTLSVFTLLAISFLNCPFIVTLNI(SEQ ID NO:180)
TM3-(86) YAIFVLYASAWLTFLSLSVFTLLAINCPFIVTLNI(SEQ ID NO:181)
TM3-(87) YAIFVLYASAWLTFLNPFSLSVFSLLAIIVTLNI(SEQ ID NO:182)
TM3-(88) YAIFVLYASAWLSFLNLGGVTASFTASVGPFIVTLNI(SEQ ID NO:183)
TM3-(89) YAIFVLYASAWLSFLNLGGVTASFTASVGVTLNI(SEQ ID NO:184)
TM3-(90) YAIFVLLGGVTASFTASVNYASAWLSFLNCPFIVTLNI(SEQ ID NO:185)
TM3-(91) YAIFVLYAIFFFLLFSAWLSFLNCPFIVTLNI(SEQ ID NO:186)
TM3-(92) YAIFVLYASAWLSFLNCPFIVTLNIIFFFLLFIVTLNI(SEQ ID NO:187)
TM3-(93) YAIFVLYASAWIFFFLLFLSFLNCPFIVTLNI(SEQ ID NO:188)
TM3-(94) YAIFVLYASAWLFFTVLASELSVYTLTVSFLNCPFIVTLNI(SEQ ID NO:189)
TM3-(95) YAIFVLYASAWLSFLFATLGGEIALCPFIVTLNI(SEQ ID NO:190)
TM3-(96) YAIFVLYAFATLGGEIALSAWLSFLNCPFIVTLNI(SEQ ID NO:191)
TM3-(97) YAIFFTVLASELSVYTLTVYASAWLSFLNCPFIVTLNI(SEQ ID NO:192)
TM3-(98) YAIFFPIAALFASIASAWLSFLNCPFIVTLNI(SEQ ID NO:193)
TM3-(99) YAIFVLYASAWLSFFPIAALFASIPFIVTLNI(SEQ ID NO:194)
TM3-(100) YAIFVLYASAWLSFLNCPFFPIAALFASILNI(SEQ ID NO:195)
TM3-(101) YAIFVLYASAWLSLDVLFSTASIMHLSFLNGGEIALWSLIVTLNI(SEQ ID NO:196)
TM3-(102) YAIFVLYASLDVLFSTASIMHLIALWSLNCPFIVTLNI(SEQ ID NO:197)
TM3-(103) YAIFVLYAGGEIALWSLSFLNSLDVLFSTASIMHLPFIVTLNI(SEQ ID NO:198)
TM3-(104) YAIFVLYASAWLSFFDVLFSTASIMHLFGYLGNFLLNCPFIVTLNI(SEQ ID NO:199)
TM3-(105) YAIFVLYASAWLFFFLLFGYLSLDVLFSTASIMHLGNFLLPFIVTLNI(SEQ ID NO:200)
TM3-(106) YAIFVLYASAWLSFLNTACFYVAITASLSLMHLFITEIALIPFIVTLNI(SEQ ID NO:201)
TM3-(107) YASLDVLFSTAIMHLSAWLTACFYVAITASLCFITEIALICPFIVTLNI(SEQ ID NO:202)
TM3-(108) YAIFVLYATACFYVAITASLSFLNCPFIVTLNISLDVLFSTASIMHL(SEQ ID NO:203)
TM3-(109) YAITACFYVAITASLCFITEIALIASAWLSFLNCPFIVTLNI(SEQ ID NO:204)
TM3-(110) YAIFVLYATACFYSTASILNLIMHLCAISLVAIITEIALISAWLSFLN(SEQ ID NO:205)
TM3-(111) YAIFVLYASAWLSFLNACFYICLFASILNLIMHLGVCFLIPFIVTLNI(SEQ ID NO:206)

TM3-(112) YAIFVLYASAWNASILNLIMHLCFYICLFAGVMLILSFLNCPFIVTLNI(SEQ ID NO:207)
TM3-(113) YAIFPFVQCVVSIFSLVLIAVVLYFYIAGVCFLIASAWLSFLNCPFIVTI(SEQ ID NO:208)
TM3-(114) PFVQCVSITVSIFSLVLIAVYAIFVLYASVDAVNMFTSAWCPFIVTLNI(SEQ ID NO:209)
TM3-(115) YAIFGDWSSVDAVNMFTVLYASAWLSFLNCPFIVTLNI(SEQ ID NO:210)
TM3-(116) YAIFVLYAGDWSSAWLSVDAVNMFTSFLNCPFIVTLNI(SEQ ID NO:211)
TM3-(117) YAIFVLYASAWLGDWSSFLNSVDAVNMFTPFIVTLNI(SEQ ID NO:212)
TM3-(118) YAIFVLYASAWLSFLNCPFIVGDWSSVDAVNMFTTLNI(SEQ ID NO:213)
TM3-(119) YAIFVLYASAWLGYLGSVDMFTSFLNCPFIVTGDWSLNI(SEQ ID NO:214)
TM3-(120) YAISVDAVNMFTFVLYAGYLGSAWLSFLNCPFIVTLNI(SEQ ID NO:215)
TM3-(121) YAIFSLSVFSLLAIVLYASAWLGYLGSFLNCPFIVTLNI(SEQ ID NO:216)
TM3-(122) YAIFVLYAGYLGAGNMDSLSVFSLLAISAWLSFLNCPFIVTLNI(SEQ ID NO:217)
TM3-(123) YAIFVLYASAWLSLSVFGNMSLLAISFLNCPFIVTLNI(SEQ ID NO:218)
TM3-(124) YAIFVLYASAWLSFLSLSVFGGSLLAINCPFIVTLNI(SEQ ID NO:219)
TM3-(125) YAIFVLYASAWLSFLNPFSLSVFGSLLAIIVTLNI(SEQ ID NO:220)
TM3-(126) YAIFVLYATAWLTFLSLANCVTATIPFIVTLNI(SEQ ID NO:221)
TM3-(127) YAIFVLYATAWLSFLNCTSLASSIVVTATIVTLNI(SEQ ID NO:222)
TM3-(128) YAIFVLYATAWLSFLNVTLNISLACTTTIV(SEQ ID NO:223)
TM3-(129) YAIFVLYATAWLTFLNTATILSLANLMFIVTLNI(SEQ ID NO:224)
TM3-(130) YAIFVLYATAWLSFLNMATILNLPFSVDAVIVTLNI(SEQ ID NO:225)

Recently discovered G-proteins also can be used according to the presently claimed invention to provide GPR polypeptides of the present invention, based on the teaching and guidance presented herein. Exampled of such GPR polypeptides of the present invention may include, as non-limiting examples, GPR polypeptides corresponding to transmembrane domain III, e.g., as follows:

TM3-(131) ISTMYTVTGRWTLGQVVCDFWLSSDITCCTASILHLCVIAL (SEQ ID NO:226)
TM3-(132) ILYGYRWPLPSKLCAVWIYLDVLFSTASIMHLCAISL (SEQ ID NO:227)
TM3-(133) IIYI VMDRWKLGYFLCEVWLSVDMTCCTCSILHLCVIAL (SEQ ID NO:228)
TM3-(134) IADKTVRVAMGAENDLGYNFRSDDVCGHCWQWYCSL (SEQ ID NO:229)
TM3-(135) ILNYWPFGLALCHFVNYSQAVSVLVSAYTLVAISI (SEQ ID NO:230)
TM3-(136) ILGRWEFGIHLCKLWLTCDVLCCTSSILNLCAIALD (SEQ ID NO:231)
TM3-(137) IMASVMHRHCLPLIGICLSSERHCLVSIFVELGAL (SEQ ID NO:232)

Further non-limiting examples of consensus GPR polypeptides for transmembrane domain III of several or many, such as 1-500, or any range or value therein, more recently discovered G-protein receptors are as follows:

TM3-(138) YAIFVLYASAWLSFLNCPFISILHLCVIALVTLNI(SEQ ID NO:233)
TM3-(139) YAIFVLYATAWLSFLNCPFISILNLCAIALDVTLNI(SEQ ID NO:234)

TM3-(140) YAIFVLYATAWLTFLNCPFISIFVELGALVTLNI(SEQ ID NO:235)
TM3-(141) YAIFVLYASAWLTFLNCPFISIFVELSIMHLCAISLGALVTLNI(SEQ ID NO:236)
TM3-(142) WAIFVLYAILGRWEFGIHLCKLWLTSAWLSIMHLCAISLSFLNCPFIVTLNI(SEQ ID NO:237)
TM3-(143) WAIFVLYAILGRWEFGIHLCKLWLTTAWLSIMHLCAISLSFLNCPFIVTLNI(SEQ ID NO:238)
TM3-(144) WAIFVLYATAWLTFLNCPFSIMHLCAISLIVTLNI(SEQ ID NO:239)
TM3-(145) WAIFVLYASAWLTFLNCPFISIMHLCAISLVTLNI(SEQ ID NO:240)
TM3-(146) YAVFVLYASAWLSFLNMSIMHLCAISLPFIVTLNI(SEQ ID NO:241)
TM3-(147) YAVFVLYATAWLSFLNMPFSILNLCAIALDIVTLNI(SEQ ID NO:242)
TM3-(148) YAVFVLYATAWLSILNLCAIALDTFLNMPFIVTLNI(SEQ ID NO:243)
TM3-(149) YAVFVLYASILNLCAIALDSAWLTFLNMPFIVTLNI(SEQ ID NO:244)
TM3-(150) YAIFVLYASAWLSFLNCVTASIPFCLVSIFVELGALIVTLNI(SEQ ID NO:245)
TM3-(151) YAIFVLYASAWLSFLNCLVSIFVELGALIVVTASIVTLNI(SEQ ID NO:246)
TM3-(152) YAIFVLYASAWLSFLNVTLNCLVSIFVELGALII(SEQ ID NO:247)
TM3-(153) YAIFVLYASAWLSFLNTASILNLMFICLVSIFVELGALVTLNI(SEQ ID NO:248)
TM3-(154) YAIFVLYASAWLSFLNMASILNLPFCLVSIFVELGALVTLNI(SEQ ID NO:249)
TM3-(155) YAIFVLYASAWLSFLNILGRWEFGIHLCKLWLTCDVLCCTSSGILLLAPFIVTLNI(SEQ ID NO:250)
TM3-(156) YAIFVLYASAWLSFLNMILGRWEFGIHLCKLWLTCDVLCCTSSGILLLAPFIVTLNI(SEQ ID NO:251)
TM3-(157) YAIFVLYASAWLILGRWEFGIHLCKLWLTCDVLCCTSSFLNSELSVYTLTVCPFIVTLNI(SEQ ID NO:252)
TM3-(158) YAIFVLYAILGRWEFGIHLCKLWLTCDVLCCTSSAWLSFLNMSELSVYTLTVPFIVTLNI(SEQ ID NO:253)
TM3-(159) YAIFVLYASAWLASRWPLPLSVYTLTVSFLNCPFIVTLNI(SEQ ID NO:254)
TM3-(160) YAIFVLYASAWLASELILYYWRWPLPCLHDLVWLCTCSILHLCVIALSVYTLTVPFIVTLNI(SEQ ID NO:255)
TM3-(161) YAIFVLYASAWLSFLASELSVYASELSSTLHDLVWLWLDVFCVIALTTVNMPFIVTLNI(SEQ ID NO:256)
TM3-(162) YAIFVLYASAWLSFLNGGEIALWSLCPFIILYYWRWPLPCLHDLVSILHLCVIALVTLNI(SEQ ID NO:257)
TM3-(163) YVWLWLDVFCCTCSILHLCVIALFVLYASAWLSFLNGGEIALWSLIVTLNI(SEQ ID NO:258)
TM3-(164) YAIFVLYASAWLAIILYYWRWPLPCLHDLGGEIALWSLNCPFIVTLNI(SEQ ID NO:259)

Non-limiting examples of consensus GPR polypeptides for domain V across several or many, such as 1-500, or any range or value therein, G-protein receptors are as follows:

TM5-(1) CDVFVFVDIMLCTASIFNLCAISVG(SEQ ID NO:260)
TM5-(2) YAIFVLYDIMLCTASIFNLCAISVG(SEQ ID NO:261)
TM5-(3) DYAIFVFVDIMLMTASIFNLMAISVG(SEQ ID NO:262)
TM5-(4) DYAIFVFVDIMLHTTASTIFNLMATITVG(SEQ ID NO:263)
TM5-(5) CDVAVVYSSDIMLFYVCTASIFSSNLCAISSVG(SEQ ID NO:264)
TM5-(6) FLFCSLGSFYIPIAVILVDIMLCTASIFNLCAISVG(SEQ ID NO:265)
TM5-(7) YAIFVLYDFLFCSLGSFYIPIAVILIMLCTASIFNLCAISVG(SEQ ID NO:266)
TM5-(8) DYAIFVFVDIMLMTASIFLFCSLGSFYIPIAVILISVG(SEQ ID NO:267)
TM5-(9) DYAIFVFVDIMLHTTASTIFNLMAFLFCSLGSFYIPIAVILTITVG(SEQ ID NO:268)

TM5-(10) CDVAVVYSSDIMLFYVCTASIFSSNLFLFCSLGSFYCAISSVG(SEQ ID NO:269)
TM5-(11) CDVFVFVDIMLCTASIFNWYILSSIGSFFAPCLILLVYLLCAISVG(SEQ ID NO:270)
TM5-(12) YAIFVLYDIMLCTASIFNLCAIWYILSSIGSFFAPCLILLVYLSVG(SEQ ID NO:271)
TM5-(13) DYAIFVFVDIWYILSSIGSFFAPCLILLVYLASIFNLMAISVG(SEQ ID NO:272)
TM5-(14) DYAIWYILSSIGSFFAPCLILLVYLIMLHTTASTIFNLMATITVG(SEQ ID NO:273)
TM5-(15) CDVAVVYSSDIMLFYVCWYILSSIGSFFAPCLILLVYLSSNLCAISSVG(SEQ ID NO:274)
TM5-(16) CDVFVFVDIMLCTASIFWYVISSSIGSFFAPCLINHLVYNLCAISVG(SEQ ID NO:275)
TM5-(17) YAIFVLYDIMLCTASIFNLCAIWYVISSSIGSFFAPCLINHLVYSVG(SEQ ID NO:276)
TM5-(18) DYAIFVFVWYVISSSIGSFFAPCLINHLVYDIMLMTASIFNLMAISVG(SEQ ID NO:277)
TM5-(19) DYAIFVFVDIMLHTTASTIFWYVISSSIGSFFAPCLINHLVYTVG(SEQ ID NO:278)
TM5-(20) CDVAVVYSSDIMLFYVCTASIFSWYVISIGSFFAINHLVYNLCAISSVG(SEQ ID NO:279)
TM5-(21) CDVFVFVDIMLCTASIFNLCAITYAISSSVISFYIPVAILVTYT(SEQ ID NO:280)
TM5-(22) YAIFVLYDIMLCTATYAISSSVISFYIPVAILVTYTSIFNLCAISVG(SEQ ID NO:281)
TM5-(23) DYAIFVFVDIMLMTATYAISSSVISFYIPVAILVTYTISVG(SEQ ID NO:282)
TM5-(24) TYAISSSVISFYIPVATDYAIFVFVDIMLHTTASTIFNLMATITVG(SEQ ID NO:283)
TM5-(25) CDVAVVYSSDIMLFYVCTATYAISSSVISFYIPVAILVTYTSSVG(SEQ ID NO:284)
TM5-(26) CDVFVFVDFVIYSSVVSFYLPFGVTVLVYACTASIFNLCAISVG(SEQ ID NO:285)
TM5-(27) YAIFVLYDFVIYSSVVSFYLPFGVTVLVYASIFNLCAISVG(SEQ ID NO:286)
TM5-(28) DYAIFVFVDFVIYSSVVSFYLPFGVTVLVYATASIFNLMAISVG(SEQ ID NO:287)
TM5-(29) DYAIFVFVDFVIYSSVVSFYLPFGVTVLVYAHTTASTIFNLMATITVG(SEQ ID NO:288)
TM5-(30) CDVAVVYSSDFVIYSSVVSFYLPFGVTVYVCTASIFSSNLCAISSVG(SEQ ID NO:289)
TM5-(31) CDVFVFVDIMLCTASYTIYSTCGAFYIPSVLLIILYGNLCAISVG(SEQ ID NO:290)
TM5-(32) YAIFVLYDIMLCTASYTIYSTCGAFYIPSVLLIILYGNLCAISVG(SEQ ID NO:291)
TM5-(33) DYAIFVFVDIMLMTASYTIYSTCGAFYIPSVLLIILYGNLMAISVG(SEQ ID NO:292)
TM5-(34) DYAIFVFVDIMLHTTASYTIYSTCGAFYIPSVLLIILYGMATITVG(SEQ ID NO:293)
TM5-(35) CDVAVVYSSDIMSYTIYSTCGAFYIPSVLLIILYGIFSSNLCAISSVG(SEQ ID NO:294)
TM5-(36) CDVFVFFVLIGSFVAVDIMLCTASIFNLCAISVG(SEQ ID NO:295)
TM5-(37) YAIFVLYFVLIGSFVADIMLCTASIFNLCAISVG(SEQ ID NO:296)
TM5-(38) DYAIFVFVFVLIGSFVADIMLMTASIFNLMAISVG(SEQ ID NO:297)
TM5-(39) DYAIFVFVFVLIGSFVADIMLHTTASTIFNLMATITVG(SEQ ID NO:298)
TM5-(40) CDVAVVYSSFVLIGSFVADIMLFYVCTASIFSSNLCAISSVG(SEQ ID NO:299)
TM5-(41) CDVFVFVDIMLCFFIPTLIMVITYFNLCAISVG(SEQ ID NO:300)
TM5-(42) YAIFVLYDIMLCFFIPTLIMVITYFFNLCAISVG(SEQ ID NO:301)
TM5-(43) DYAIFVFVDIMLMFFIPTLIMVITYFNLMAISVG(SEQ ID NO:302)
TM5-(44) DYAIFVFVDIMLHTFFIPTLIMVITYFNLMATITVG(SEQ ID NO:303)
TM5-(45) CDVAVVYSSDIMLFYVCFFIPTLIMVITYFSSNLCAISSVG(SEQ ID NO:304)
TM5-(46) CDVVYGLVDGLVTFYLPLLIMCITYYDIMLCTASIFNLCAISVG(SEQ ID NO:305)
TM5-(47) YAIVYGLVDGLVTFYLPLLIMCITYYDIMLCTASIFNLCAISVG(SEQ ID NO:306)
TM5-(48) DYAIVYGLVDGLVTFYLPLLIMCITYYDIMLMTASIFNLMAISVG(SEQ ID NO:307)
TM5-(49) DYAIVYGLVDGLVTFYLPLLIMCISSDIMLHTTASTIFNLMATITVG(SEQ ID NO:308)
TM5-(50) CDVVYDGLVTFYLPLLIMCITYYDIMLFYVCTASIFSSNLCAISSVG(SEQ ID NO:309)
TM5-(51) CDVFVFVDIMLLVIFLGLVIVIPFVLIIVSYASIFNLCAISVG(SEQ ID NO:310)
TM5-(52) YAIFVLYDIMLLVIFLGLVIVIPFVLIIVSYAIFNLCAISVG(SEQ ID NO:311)
TM5-(53) DYAIFVFVDIMLMLVIFLGLVIVIPFVLIIVSYAIFNLMAISVG(SEQ ID NO:312)
TM5-(54) DYAIFVFVDIMLHTLVIFLGLVIVIPFVLIIVSYAIFNLMATITVG(SEQ ID NO:313)

TM5-(55) CDVAVVYSSDIMLFLVIFLGLVIVIPFVLIIVSYAIFSSNLCAISSVG(SEQ ID NO:314)
TM5-(56) CDVFVFVDIMLCTALMIYILGGLIIIIPFLLIVMSYVSIFNLCAISVG(SEQ ID NO:315)
TM5-(57) YAIFVLYDIMLCTALMIYILGGLIIIIPFLLIVMSYVSIFNLCAISVG(SEQ ID NO:316)
TM5-(58) DYAIFVFVDIMLMTASIFNLMIYILGGLIIIIPFLLIVMSYVLMAISVG(SEQ ID NO:317)
TM5-(59) DYAIFVFVDIMLHTTASTILMIYILGGLIIIIPFLLIVMSYVITVG(SEQ ID NO:318)
TM5-(60) CDVAVVYSSDIMLFYVCTAYILGGLIPFLLIVMTYVSIFTNLCAISSVG(SEQ ID NO:319)
TM5-(61) CDVFVFVDIMLCTASIFNLLMIHIMEVIIIVIPFVLIVISYACAISVG(SEQ ID NO:320)
TM5-(62) YAIFVLYDIMLCTASIFNLLMIHIMEVIIIVIPFVLIVISYACAISVG(SEQ ID NO:321)
TM5-(63) DYAIFVFVDIMLMTASIFLMIHIMEVIIIVIPFVLIVISYAISVG(SEQ ID NO:322)
TM5-(64) DYAIFVFVDIMLHTTASTILMIHIMEVIIIVIPFVLIVISYAITVG(SEQ ID NO:323)
TM5-(65) CDVAVVYSSDIMLFYVCTASIFLMIHIMEVIIIVIPFVLIVISYAAISSVG(SEQ ID NO:324)

Non-limiting examples of longer consensus GPR polypeptides for domain V across several or many, such as 1-500, or any value or range therein, G-protein receptors are as follows:

T M 1 - (1)
TM1NWPALSIVVIIINTIGGNILVIMAVSIYTSLDVMLCTASILNLLISLFVLIGSFVAFFIPLTIMVITYFLFNVFFVW
IGYVCSSSLGINPVIIYTLF(SEQ ID NO:325)

T M 1 - (2)
NWPALSIVVIIINTIGGNILVIMAVTIYTTLDVMLCTATILNLLISLFVLIGTFVAFFIPLTIMVITYFLFNVFFVWIGY
VCTTTLGINPVIIYTLF(SEQ ID NO:326)

T M 1 - (3)
NWPALTIVVIIINTIGGNILVIMAVSIYTTLDVMLCTATILNLLITLFVLIGTFVAFFIPLTIMVITYFLFNVFFVWIGY
VCSTSLGINPVIIYTLF(SEQ ID NO:327)

T M 1 - (5)
NWPALTIVVIIINTIGGNILVIMAVTIYTTLDVMLCTATILNLLITLFVLIGTFVAFFIPLTIMVITYFLFNVFFVWIGY
VCTLGINPVIIYTLF(SEQ ID NO:328)

T M 1 - (6)
NWKNWSALLTTVVIILTIAGNILVIMAVSSLDVMLCTASILNLLISLFVLIGSFVAFFIPLTIMVITYFLFNVFFVWIGY
VCSSSLGINPVIIYTLF(SEQ ID NO:329)

T M 1 - (7)
ITITVVLAVLILITVAGNVVVCIAVGSIYTSLDVMLCTASILNLLISLFVLIGSFVAFFIPLTIMVITYFLFNVFFVWIG
YVCSSSLGINPVIIYTLF(SEQ ID NO:330)

T M 1 - (8)
TLTLVCIACLUSLTVFGNVLVIIAVFSLDVMLCTASILNLLISLFVLIGSFVAFFIPLTIMVITYFLFNVFFVWIGYVCS
SSLGINPVIIYTLF(SEQ ID NO:331)

T M 1 - (9)
TAAIAAAITFLILFTIFGNALVIIAVLSIYTSLDVMLCTASILNLLISLFVLIGSFVAFFIPLTIMVITYFLFNVFFVWI
GYVCSSSLGINPVIIYTLF(SEQ ID NO:332)

T M 1 - (1 0)
AISVGLVLGAFILFAIVGNILVILSVANWPALSIVVIIINTIGGNILVIMAVSIYTSLDVMLCTASILNLLISLFVLIGS
FVAFFIPLTIMVITYFLFNVFFVWIGYVCSSSLGINPVIIYTLF(SEQ ID NO:333)

T M 1 - (1 1)
AALAGALLALAVLATVGGNLLVIVAIASLDVMLCTASILNLLISLFVLIGSFVAFFIPLTIMVITYFLFNVFFVWIGYVC
SSSLGINPVIIYTLF(SEQ ID NO:334)
T M 1 - (1 2)
TAGDCLIMLIVLLIVAGNVLVIVAISLDVMLCTASILNLLISLFVLIGSFVAFFIPLTIMVITYFLFNVFFVWIGYVCSS
SLGINPVIIYTLF(SEQ ID NO:335)
T M 1 - (1 3)
VITIAVVTAVVSLMTIVGNVLVMISFSIYTSLDVMLCTASILNLLISLFVLIGSFVAFFIPLTIMVITYFLFNVFFVWIG
YVCSSSLGINPVIIYTLF(SEQ ID NO:336)
T M 1 - (1 4)
MVFIATVRGSLSLVTVVGNILVMLSISIYTSLDVMLCTASILNLLISLFVLIGSFVAFFIPLTIMVITYFLFNVFFVWIG
YVCSSSLGINPVIIYTLF(SEQ ID NO:337)
T M 1 - (1 5)
WFIAFLTGILALVTIIGNILVIVSFSIYTSLDVMLCTASILNLLISLFVLIGSFVAFFIPLTIMVITYFLFNVFFVWIGY
VCSSSLGINPVIIYTLF(SEQ ID NO:338)

Non-limiting examples of longer consensus GPR polypeptides for domain V across several or many, such as 1-500, or any value or range therein, G-protein receptors are as follows:

T M 3 - (1 6 5)
NWPALSIVVIIINTIGGNILVIMAFFACFVLVLTQSSIFSLLAIAINLLISLFVLIGSFVAFFIPLTIMVITYFLFNVFF
VWIGYVCSSSLGINPVIIYTLF(SEQ ID NO:339)
T M 3 - (1 6 6)
NWPALSIVVIIINTIGGNILVIMAFFACFVLVLTQSSIFSLLAIAIFVLIGSFVAFFIPLTIMVITYFLFNVFFVWIGYV
CSSSLGINPVIIYTLF(SEQ ID NO:340)
T M 3 - (1 6 7)
NWPALSIVVIIINTIGGNILVIMAVMVACPVLILTQSSIIALLAIAVSFVAFFIPLTIMVITYFLFNVFFVWIGYVCSSS
LGINPVIIYTLF(SEQ ID NO:341)
T M 3 - (1 6 8)
NWPALSIVVIIINTIGGNILVIMAVLWLALDYVASNASVLNLLLISFFFIPLTIMVITYFLFNVFFVWIGYVCSSSLGIN
PVIIYTLF(SEQ ID NO:342)
T M 3 - (1 6 9)
NWPALSIVVIIINTIGGNILVIMAVLYVVSNASVMNLLIISSFVAFFIPLTIMVITYFLFNVFFVWIGYVCSSSLGINPV
IIYTLF(SEQ ID NO:343)
T M 3 - (1 7 0)
NWPALSIVVIIINTIGGNILVIMAVLWIAIDYVASNASVLNLLVISFGSFVAFFIPLTIMVITYFLFNVFFVWIGYVCSS
SLGINPVIIYTLF(SEQ ID NO:344)
T M 3 - (1 7 1)
NWPALSIVVIIINTIGGNILVIMAVLFPFLQKSSVGITVLNLCALSGSFVAFFIPLTIMVITYFLFNVFFVWIGYVCSSS
LGINPVIIYTLF(SEQ ID NO:345)
T M 3 - (1 7 2)
NWPALSIVVIIINTIGGNILVIMAVCITYLQYLGINASSCSITAFTIIGSFVAFFIPLTIMVITYFLFNVFFVWIGYVCS
SSLGINPVIIYTLF(SEQ ID NO:346)

T M 3 - (1 7 3)
NWPALSIVVIIINTIGGNILVIMAVFHNFFPIAALFASIYSMTAVAGSFVAFFIPLTIMVITYFLFNVFFVWIGYVCSSS
LGINPVIIYTLF(SEQ ID NO:347)
T M 3 - (1 7 4)
NWPALSIVVIIINTIGGNILVIMAVIASASVSFNLYASVFLLTCLSIGSFVAFFIPLTIMVITYFLFNVFFVWIGYVCSS
SLGINPVIIYTLF(SEQ ID NO:348)

As another non-limiting, illustrative example of a GPR polypeptide consensus sequences across each individual or different transmembrane domains of 5-HT receptors may be made, such as for 5-HT, as the following:

5HT consensus(4) KNASALLSVIIINSIGGNVVTAVS (SEQ ID NO:349);

5HT consensus(5) YFLMSLAVTDLVVSFVMPVSAL (SEQ ID NO:350);

5HT consensus(6) AITKIAITWAISGVSVPFIPVWG (SEQ ID NO:351); and

5HT consensus(7) LGIIFGTFIIIWLPFFITNLVSPI (SEQ ID NO:352);

Wherein variations and substitutions of amino acids may be made as described herein.

Alternatively, 5-HT consensus sequences may be provided as consensus peptides of the present invention as consensus peptides for individual transmembrane domains, such as 5-HT domains III, V and VII, e.g., as follows:

5-HT consensus (8): IWISLDVLFSTASSIMHLCAISL (SEQ ID NO:353)

5-HT consensus (9): GYTIYSTLVTFYIPSVIMVITYG (SEQ ID NO:354)

5-HT consensus (10): LLNFFNWIGYLNSLINPVIYTLF (SEQ ID NO:355)

This invention is also directed to an antibody which binds an epitope specific for a GPR polypeptide of the present invention and the use of such an antibody to detect the presence of, or measure the quantity or concentration of, the GPR protein in a cell, a cell or tissue extract, a biological fluid, an extract thereof, a solution, or sample, *in vitro*, *in situ*, or *in vivo*.

The term "antibody" is meant to include polyclonal antibodies, monoclonal antibodies (mAbs), chimeric antibodies, anti-idiotypic (anti-Id) antibodies to antibodies specific for GPR polypeptide of the present invention, as well as fragments, consensus polypeptides or chemical derivatives thereof.

Polyclonal antibodies are heterogeneous populations of antibody molecules derived from the sera of animals immunized with an antigen.

A monoclonal antibody contains a substantially homogeneous population of antibodies specific to antigens, which population contains substantially similar epitope binding sites. MAbs may be obtained by methods known to those skilled in the art. See, for example Kohler and Milstein, *Nature* 256:495-497 (1975); U.S. Patent No. 4,376,110; Ausubel et al, eds., *Current Protocols in Molecular Biology*, Wiley Interscience, N.Y., (1987, 1992); and Harlow and Lane *Antibodies: A Laboratory Manual* Cold Spring Harbor Laboratory (1988), the contents of which references are incoporated entirely herein by reference. Such antibodies may be of any immunoglobulin class including IgG, IgM, IgE, IgA, GILD and any subclass thereof. A hybridoma producing a mAb of the present invention may be cultivated *in vitro*, *in situ* or *in vivo*. Production of high titers of mAbs *in vivo* or *in situ* makes this the presently preferred method of production.

Chimeric antibodies are molecules different portions of which are derived from different animal species, such as those having variable region derived from a murine mAb and a human immunoglobulin constant region, which are primarily used to reduce immunogenicity in application and to increase yields in production, for example, where murine mAbs have higher yields from hybridomas but higher immunogenicity in humans, such that human/murine chimeric mAbs are used. Chimeric antibodies and methods for their production are known in the art (Cabilly et al, *Proc. Natl. Acad. Sci. USA* 81:3273-3277 (1984); Morrison et al., *Proc. Natl. Acad. Sci. USA* 81:6851-6855 (1984); Boulianne et al., *Nature* 312:643-646 (1984); Cabilly et al., *European Patent Application 125023* (published November 14, 1984); Neuberger et al., *Nature* 314:268-270 (1985); Taniguchi et al., *European Patent Application 171496* (published February 19, 1985);

Morrison et al., *European Patent Application 173494* (published March 5, 1986); Neuberger et al., *PCT Application WO 86/01533*, (published March 13, 1986); Kudo et al., *European Patent Application 184187* (published June 11, 1986); Morrison et al., *European Patent Application 173494* (published March 5, 1986); Sahagan et al., *J. Immunol.* 137:1066-1074 (1986); Robinson et al., *International Patent Publication No.PCT/US86/02269* (published 7 May 1987); Liu et al., *Proc. Natl. Acad. Sci. USA* 84:3439-3443 (1987); Sun et al., *Proc. Natl. Acad. Sci. USA* 84:214-218 (1987); Better et al., *Science* 240:1041- 1043 (1988); and Harlow and Lane *Antibodies: A Laboratory Manual* Cold Spring Harbor Laboratory (1988)). These references are incorporated entirely herein by reference.

An anti-idiotypic (anti-Id) antibody is an antibody which recognizes unique determinants generally associated with the antigen-binding site of an antibody. An Id antibody can be prepared by immunizing an animal of the same species and genetic type (e.g., mouse strain) as the source of the mAb with the mAb to which an anti-Id is being prepared. The immunized animal will recognize and respond to the idiotypic determinants of the immunizing antibody by producing an antibody to these idiotypic determinants (the anti-Id antibody). See, for example, U.S. patent No. 4,699,880, which is herein entirely incorporated by reference.

The anti-Id antibody may also be used as an "immunogen" to induce an immune response in yet another animal, producing a so-called anti-anti-Id antibody. The anti-anti-Id may be epitopically identical to the original mAb which induced the anti-Id. Thus, by using antibodies to the idiotypic determinants of a mAb, it is possible to identify other clones expressing antibodies of identical specificity.

Accordingly, mAbs generated against a GPR polypeptide of the present invention may be used to induce anti-Id antibodies in suitable animals, such as BALB/c mice. Spleen cells from such immunized mice are used to produce anti-Id hybridomas secreting anti-Id mAbs. Further, the anti-Id mAbs can be coupled to a immunogenic carrier such as keyhole limpet hemocyanin (KLH) or cationized bovine serum albumin and used to immunize additional BALB/c mice. Sera from these mice will contain anti-anti-Id antibodies that have the binding

properties of the original mAb specific for a GPR polypeptide epitope.

The anti-Id mAbs thus have their own idiotypic epitopes, or "idiotopes" structurally similar to the epitope being evaluated.

The term "antibody" is also meant to include both intact molecules as well as fragments thereof, such as, for example, Fab and $F(ab')_2$, which are capable of binding antigen. Fab and $F(ab')_2$ fragments lack the Fc fragment of intact antibody, clear more rapidly from the circulation, and may have less non-specific tissue binding than an intact antibody (Wahl et al., *J. Nucl. Med.* 24:316-325 (1983)).

It will be appreciated that Fab and $F(ab')_2$ and other fragments of the antibodies useful in the present invention may be used for the detection and quantitation of a GPR polypeptide according to the methods disclosed herein for intact antibody molecules. Such fragments are typically produced by proteolytic cleavage, using enzymes such as papain (to produce Fab fragments) or pepsin (to produce $F(ab')_2$ fragments).

An antibody is said to be "capable of binding" a molecule if it is capable of specifically reacting with the molecule to thereby bind the molecule to the antibody. The term "epitope" is meant to refer to that portion of any molecule capable of being bound by an antibody which can also be recognized by that antibody. Epitopes or "antigenic determinants" usually consist of chemically active surface groupings of molecules such as amino acids. lipids or sugar side chains and have specific three dimensional structural characteristics as well as specific charge characteristics.

An "antigen" is a molecule or a portion of a molecule capable of being bound by an antibody which is additionally capable of inducing an animal to produce antibody capable of binding to an epitope of that antigen. An antigen may have one, or more than one epitope. The specific reaction referred to above is meant to indicate that the antigen will react, in a highly selective manner, with its corresponding antibody and not with the multitude of other antibodies which may be evoked by other antigens.

The antibodies, or fragments of antibodies, useful in the present invention may be used to quantitatively or qualitatively

detect a GPR polypeptide in a sample or to detect presence of cells which express a GPR polypeptide of the present invention. This can be accomplished by immunofluorescence techniques employing a fluorescently labeled antibody (see below) coupled with light microscopic, flow cytometric, or fluorometric detection.

The antibodies (of fragments thereof) useful in the present invention may be employed histologically, as in immunofluorescence or immunoelectron microscopy, for *in situ* detection of a GPR polypeptide of the present invention. *In situ* detection may be accomplished by removing a histological specimen from a patient, and providing the a labeled antibody of the present invention to such a specimen. The antibody (or fragment) is preferably provided by applying or by overlaying the labeled antibody (or fragment) to a biological sample. Through the use of such a procedure, it is possible to determine not only the presence of a GPR polypeptide but also its distribution on the examined tissue. Using the present invention, those of ordinary skill will readily perceive that any of wide variety of histological methods (such as staining procedures) can be modified in order to achieve such *in situ* detection.

Such assays for a GPR polypeptide of the present invention typically comprise incubating a biological sample, such as a biological fluid, a tissue extract, freshly harvested cells such as lymphocytes or leukocytes, or cells which have been incubated in tissue culture, in the presence of a detectably labeled antibody capable of identifying a GPR polypeptide, and detecting the antibody by any of a number of techniques well-known in the art. See, e.g., Harlow and Lane, supra; Ausubel et al, supra; and Sambrook et al, supra.

The biological sample may be treated with a solid phase support or carrier, such as nitrocellulose, or other solid support or carrier which is capable of immobilizing cells, cell particles or soluble proteins. The support or carrier may then be washed with suitable buffers, followed by treatment with a detectably labeled GPR polypeptide-specific antibody. The solid phase support or carrier may then be washed with the buffer a second time to remove unbound antibody. The amount of bound label on said solid support or carrier

may then be detected by known method steps, see, e.g., Harlow, supra; Ausubel, supra; or Sambrook, supra.

By "solid phase support", "solid phase carrier", "solid support", "solid carrier", "support" or "carrier" is intended any support or carrier capable of binding antigen or antibodies. Well-known supports or carriers, include glass, polystyrene, polypropylene, polyethylene, dextran, nylon amylases, natural and modified celluloses, polyacrylamides, gabbros, and magnetite. The nature of the carrier can be either soluble to some extent or insoluble for the purposes of the present invention. The support material may have virtually any possible structural configuration so long as the coupled molecule is capable of binding to an antigen or antibody. Thus, the support or carrrier configuration may be spherical, as in a bead, or cylindrical, as in the inside surface of a test tube, or the external surface of a rod. Alternatively, the surface may be flat such as a sheet, polymer test strip, etc. Preferred supports or carriers include polystyrene beads. Those skilled in the art will know many other suitable carriers for binding antibody or antigen, or will be able to ascertain the same by use of routine experimentation.

The binding activity of a given lot of anti-GPR polypeptide antibody may be determined according to well known method steps. Those skilled in the art will be able to determine operative and optimal assay conditions for each determination by employing routine experimentation. See, e.g., Harlow, supra.

Other such steps as washing, stirring, shaking, filtering and the like may be added to the assays as is customary or necessary for the particular situation.

One of the ways in which a GPR polypeptide-specific antibody, anti-idiotype antibody or fragment thereof, can be detectably labeled is by linking the same to an enzyme and use in an enzyme immunoassay (EIA). This enzyme, in turn, when later exposed to an appropriate substrate, will react with the substrate in such a manner as to produce a chemical moiety which can be detected, for example, by spectrophotometric, fluorometric or by visual means. Enzymes which can be used detectably label the antibody include, but are not limited to, malate dehydrogenase, staphylococcal nuclease,

delta-5-steroid isomerase, yeast alcohol dehydrogenase, alpha-glycerophosphate dehydrogenase, triose phosphate isomerase, horseradish peroxidase, alkaline phosphatase, asparaginase, glucose oxidase, beta-galactosidase, ribonuclease, urease, catalase, glucose-6- phosphate dehydrogenase, glucoamylase and acetylcholinesterase. The detection can be accomplished by colorimetric methods which employ a chromogenic substrate for the enzyme. Detection may also be accomplished by visual comparison of the extent of enzymatic reaction of a substrate in comparison with similarly prepared standards. See, Harlow, supra, Ausubel, supra.

Detection may be accomplished using any of a variety of other immunoassays. For example, by radioactivity labeling the antibodies or antibody fragments, it is possible to detect R-PTPase through the use of a radioimmunoassay (RIA). A good description of RIA maybe found in *Laboratory Techniques and Biochemistry in Molecular Biology*, by Work et al., North Holland Publishing Company, NY (1978) with particular reference to the chapter entitled *"An Introduction to Radioimmune Assay and Related Techniques"* by Chard, incorporated entirely by reference herein. The radioactive isotope can be detected by such means as the use of a γ-counter, a scintillation counter or by autoradiography.

It is also possible to label an anti-GPR polypeptide antibody, anti-idiotype antibody or fragment thereof, with a fluorescent compound. When the fluorescently labeled antibody is exposed to light of the proper wave length, its presence can be then be detected due to fluorescence. Among the most commonly used fluorescent labelling compounds are fluorescein isothiocyanaté, rhodamine, phycoerythrin, phycocyanin, allophycocyanin, o-phthaldehyde and fluorescamine, commercially available, e.g., from Molecular Probes, Inc. (Eugene, Ore.).

The antibody can also be detectably labeled using fluorescence emitting metals such as ^{152}EU, or others of the lanthanide series. These metals can be attached to the antibody using such metal chelating groups as diethylenetriamine pentaacetic acid (EDTA).

The antibody also can be detectably labeled by coupling it to a chemiluminescent compound. The presence of the

chemiluminescent-tagged antibody is then determined by detecting the presence of luminescence that arises during the course of a chemical reaction. Examples of particularly useful chemiluminescent labeling compounds are luminol, isoluminol, theromatic acridinium ester, imidazole, acridinium salt and oxalate ester.

Likewise, a bioluminescent compound may be used to label the antibody of the present invention. Bioluminescence is a type of chemiluminescence found in biological systems in which a catalytic protein increases the efficiency of the chemiluminescent reaction. The presence of a bioluminescent protein is determined by detecting the presence of luminescence. Important bioluminescent compounds for purposes of labeling are luciferin, luciferase and aequorin.

An antibody molecule of the present invention may be adapted for utilization in a immunometric assay, also known as a "two-site" or "sandwich" assay. In a typical immunometric assay, a quantity of unlabeled antibody (or fragment of antibody) is bound to a solid support or carrier and a quantity of detectably labeled soluble antibody is added to permit detection and/or quantitation of the ternary complex formed between solid-phase antibody, antigen, and labeled antibody.

Typical, and preferred, immunometric assays include "forward" assays in which the antibody bound to the solid phase is first contacted with the sample being tested to extract the antigen form the sample by formation of a binary solid phase antibody-antigen complex. After a suitable incubation period, the solid support or carrier is washed to remove the residue of the fluid sample, including unreacted antigen, if any, and then contacted with the solution containing an unknown quantity of labeled antibody (which functions as a "reporter molecule"). After a second incubation period to permit the labeled antibody to complex with the antigen bound to the solid support or carrier through the unlabeled antibody, the solid support or carrier is washed a second time to remove the unreacted labeled antibody.

In another type of "sandwich" assay, which may also be useful with the antigens of the present invention, the so-called "simultaneous" and "reverse" assays are used. A "simultaneous" and "reverse" assays are used. A simultaneous assay involves a single

incubation step as the antibody bound to the solid support or carrier and labeled antibody are both added to the sample being tested at the same time. After the incubation is completed, the solid support or carrier is washed to remove the residue of fluid sample and uncomplexed labeled antibody. The presence of labeled antibody associated with the solid support or carrier is then determined as it would be in a conventional "forward" sandwich assay.

In the "reverse" assay, stepwise addition first of a solution of labeled antibody to the fluid sample followed by the addition of unlabeled antibody bound to a solid support or carrier after a suitable incubation period is utilized. After a second incubation, the solid phase is washed in conventional fashion to free it of the residue of the sample being tested and the solution of unreacted labeled antibody. The determination of labeled antibody associated with a solid support or carrier is then determined as in the "simultaneous" and "forward" assays. See, e.g., for the above-mentioned immunological techniques, Harlow, supra; Ausubel et al, supra; and Sambrook et al, supra. GPR polypeptides of the present invention can be made by chemical synthesis or by recombinant methods, wherein chemical synthesis is preferred.

Synthetic production of transmembrane proteins of the present invention

GPR polypeptides, variants and chemical derivatives thereof can be synthesized according to known method steps, including portions of known GPR transmembrane domains, consensus peptides thereof, conservative substitution derivative thereof or functional derivatives thereof.

Chemical polypeptide synthesis is a rapidly evolving area in the art, and methods of solid phase polypeptide synthesis are well-described in the following references, hereby entirely incorporated by reference: (Merrifield, B., *J. Amer. Chem. Soc.* 85:2149-2154 (1963); Merrifield, B., *Science* 232:341-347 (1986); Wade, J.D. et al., *Biopolymers* 25:S21-S37 (1986); Fields, G.B., *Int. J. Polypeptide Prot. Res.* 35:161 (1990); MilliGen Report Nos. 2 and 2a, Millipore Corporation, Bedford, MA, 1987) Ausubel et al, supra, and Sambrook et al. supra.

In general, as is known in the art, such methods involve blocking or protecting reactive functional groups, such as free amino, carboxyl and thio groups. After polypeptide bond formation, the protective groups are removed (or de-protected). Thus, the addition of each amino acid residue requires several reaction steps for protecting and deprotecting. Current methods utilize solid phase synthesis, wherein the C-terminal amino acid is covalently linked to an insoluble resin particle large enough to be separated from the fluid phase by filtration. Thus, reactants are removed by washing the resin particles with appropriate solvents using an automated programmed machine The completed polypeptide chain is cleaved from the resin by a reaction which does not affect polypeptide bonds.

In the more classical method, known as the "tBoc method," the amino group of the amino acid being added to the resin-bound C-terminal amino acid is blocked with tert-butyloxycarbonyl chloride (tBoc). This protected amino acid is reacted with the bound amino acid in the presence of the condensing agent dicyclohexylcarbodiimide, allowing its carboxyl group to form a polypeptide bond the free amino group of the bound amino acid. The amino-blocking group is then removed by acidification with trifluoroacetic acid (TFA); it subsequently decomposes into gaseous carbon dioxide and isobutylene. These steps are repeated cyclically for each additional amino acid residue. A more vigorous treatment with hydrogen fluoride (HF) or trifluoromethanesulfonyl derivatives is common at the end of the synthesis to cleave the benzyl-derived side chain protecting groups and the polypeptide-resin bond.

More recently, the preferred "Fmoc" technique has been introduced as an alternative synthetic approach, offering milder reaction conditions, simpler activation procedures and compatibility with continuous flow techniques. This method was used, e.g., to prepare the peptide sequences disclosed in the present application. Here, the α-amino group is protected by the base labile 9-fluorenylmethoxycarbonyl (Fmoc) group. The benzyl side chain protecting groups are replaced by the more acid labile t-butyl derivatives. Repetitive acid treatments are replaced by deprotection with mild base solutions, e.g., 20% piperidine in dimethylformamide (DMF), and the final HF cleavage treatment is eliminated. A TFA

solution is used instead to cleave side chain protecting groups and the polypeptide resin linkage simultaneously.

At least three different polypeptide-resin linkage agents can be used: substituted benzyl alcohol derivatives that can be cleaved with 95% TFA to produce a polypeptide acid, methanolic ammonia to produce a polypeptide amide, or 1% TFA to produce a protected polypeptide which can then be used in fragment condensation procedures, as described by Atherton, E. et al., *J. Chem. Soc. Perkin Trans.* 1:538-546 (1981) and Sheppard, R.C. et al., *Int. J. Polypeptide Prot. Res.* 20:451-454 (1982). Furthermore, highly reactive Fmoc amino acids are available as pentafluorophenyl esters or dihydro-oxobenzotriazine esters derivatives, saving the step of activation used in the tBoc method.

Sequences available to use as a basis for polypeptide synthesis can be based on published sequences of G-protein coupled receptors, ligands and/or effectors, wherein the transmembrane or functional domains correspond to sections of hydrophobic or other amino acids of 5 to 100 amino acids, such as 5-10, 10-15, 15-25, 20-25, 23-27, 25-30, 28-35, 20-40, 10-40, 20-30, 30-40, 40-50, 10-80, 20-60 or 25-40 amino acids in length. Recombinant production of GPR polypeptides can be accomplished according to known method steps. Standard reference works setting forth the general principles of recombinant DNA technology include Watson, J.D. et al., *Molecular Biology of the Gene*, Volumes I and II, The Benjamin/Cummings Publishing Company, Inc., publisher, Menlo Park, CA (1987); Darnell, J.E. et al., *Molecular Cell Biology*, Scientific American Books, Inc., publisher, New York, NY (1986); Lewin, B.M., *Genes III*, John Wiley & Sons, publishers, New York, NY (1989); Old, R.W., et al., *Principles of Gene Manipulation: An Introduction to Genetic Engineering*, 2d edition, University of California Press, publisher, Berkeley, CA (1981); Ausubel et al, eds., *Current Protocols in Molecular Biology*, Wiley Interscience, publisher, New York, NY (1987, 1992); and Sambrook et al., *Molecular Cloning: A Laboratory Manual*, Second Edition, Cold Spring Harbor Laboratory, publisher, Cold Spring Harbor, NY (1989), the entire contents of which references are herein incorporated by reference.

A nucleic acid sequence encoding a GPR polypeptide of the present invention may be recombined with vector DNA in accordance with conventional techniques, including blunt-ended or staggered-ended termini for ligation, restriction enzyme digestion to provide appropriate termini, filling in of cohesive ends as appropriate, alkaline phosphatase treatment to avoid undesirable joining, and ligation with appropriate ligases. Techniques for such manipulations are disclosed, e.g., by Ausubel et al, *supra*, and are well known in the art.

A nucleic acid molecule, such as DNA, is said to be "capable of expressing" a polypeptide if it contains nucleotide sequences which contain transcriptional and translational regulatory information and such sequences are "operably linked" to nucleotide sequences which encode the polypeptide. An operable linkage is a linkage in which the regulatory DNA sequences and the DNA sequence sought to be expressed are connected in such a way as to permit gene expression as GPR polypeptides in recoverable amounts. The precise nature of the regulatory regions needed for gene expression may vary from organism to organism, as is well known in the analogous art. See, e.g., Sambrook, *supra* and Ausubel *supra*.

The present invention accordingly encompasses the expression of a GPR polypeptide, in either prokaryotic or eukaryotic cells, although eukaryotic expression is preferred.

Preferred hosts are bacterial or eukaryotic hosts including bacteria, yeast, insects, fungi, bird and mammalian cells either *in vivo*, or *in situ*, or host cells of mammalian, insect, bird or yeast origin. It is preferred that the mammalian cell or tissue is of human, primate, hamster, rabbit, rodent, cow, pig, sheep, horse, goat, dog or cat origin, but any other mammalian cell may be used.

Further, by use of, for example, the yeast ubiquitin hydrolase system, *in vivo* synthesis of ubiquitin-transmembrane polypeptide fusion proteins may be accomplished. The fusion proteins so produced may be processed *in vivo* or purified and processed *in vitro*, allowing synthesis of a GPR polypeptide of the present invention with a specified amino terminus sequence. Moreover, problems associated with retention of initiation codon-derived methionine residues in direct yeast (or bacterial) expression may be

avoided. Sabin et al., *Bio/Technol.* 7(7): 705-709 (1989); Miller et al., *Bio/Technol.* 7(7): 698-704 (1989).

Any of a series of yeast gene expression systems incorporating promoter and termination elements from the actively expressed genes coding for glycolytic enzymes produced in large quantities when yeast are grown in mediums rich in glucose can be utilized to obtain GPR polypeptides of the present invention. Known glycolytic genes can also provide very efficient transcriptional control signals. For example, the promoter and terminator signals of the phosphoglycerate kinase gene can be utilized.

Production of GPR polypeptides or functional derivatives thereof in insects can be achieved, for example, by infecting the insect host with a baculovirus engineered to express transmembrane polypeptide by methods known to those of skill. See Ausubel et al, eds. *Current Protocols in Molecular Biology*, Wiley Interscience, §§16.8-16.11 (1987, 1992).

In a preferred embodiment, the introduced nucleotide sequence will be incorporated into a plasmid or viral vector capable of autonomous replication in the recipient host. Any of a wide variety of vectors may be employed for this purpose. See, e.g., Ausubel et al, supra, §§ 1.5, 1.10, 7.1, 7.3, 8.1, 9.6, 9.7, 13.4, 16.2, 16.6, and 16.8-16.11. Factors of importance in selecting a particular plasmid or viral vector include: the ease with which recipient cells that contain the vector may be recognized and selected from those recipient cells which do not contain the vector; the number of copies of the vector which are desired in a particular host; and whether it is desirable to be able to "shuttle" the vector between host cells of different species.

Preferred prokaryotic vectors known in the art include plasmids such as those capable of replication in E. coli (such as, for example, pBR322, ColE1, pSC101, pACYC 184, πVX). Such plasmids are, for example, disclosed by Maniatis, T., et al. (*Molecular Cloning, A Laboratory Manual*, Second Edition, Cold Spring Harbor Press, Cold Spring Harbor, NY (1989); Ausubel et al, eds., *Current Protocols in Molecular Biology*, Wiley Interscience, New York, NY (1987, 1992)). Bacillus plasmids include pC194, pC221, pT127, etc. Such plasmids are disclosed by Gryczan, T. (In: *The Molecular*

Biology of the Bacilli, Academic Press, NY (1982), pp. 307-329). Suitable Streptomyces plasmids include pIJ101 (Kendall, K.J., et al., *J. Bacteriol.* 169:4177-4183 (1987)), and streptomyces bacteriophages such as ϕC31 (Chater, K.F., et al., In: *Sixth International Symposium on Actinomycetales Biology*, Akademiai Kaido, Budapest, Hungary (1986), pp. 45-54). Pseudomonas plasmids are reviewed by John, J.F., et al. (*Rev. Infect. Dis.* 8:693-704 (1986)), and Izaki, K. (*Jpn. J. Bacteriol.* 33:729-742 (1978); and Ausubel et al, supra).

The expressed protein may be isolated and purified in accordance with conventional conditions, such as extraction, precipitation, chromatography, affinity chromatography, electrophoresis, or the like. For example, the cells may be collected by centrifugation, or with suitable buffers, lysed, and the protein isolated by column chromatography, for example, on DEAE-cellulose, phosphocellulose, polyribocytidylic acid-agarose, hydroxyapatite or by electrophoresis or immunoprecipitation. Alternatively, the transmembrane polypeptide or functional derivative thereof may be isolated by the use of anti-transmembrane polypeptide antibodies. Such antibodies may be obtained by well-known methods, some of which are mentioned below. These antibodies may be immobilized on cellulose, agarose, hollow fibers, or cellulose filters by covalent chemical derivatives by methods well known to those skilled in the art.

As discussed herein, GPR polypeptides of the present invention may be further modified for purposes of drug design, such as for example to reduce immunogenicity, to prevent solubility and/or enhance delivery, or to prevent clearance or degradation.

Appropriate modification of the primary amino acid sequence of GPR polypeptides of the present invention, obtained by mutagenesis or utilizing fragments of other related forms of G-protein transmembrane proteins, as described herein, will allow the creation of molecules which bind G-protein coupled receptors with higher affinity than that exhibited by naturally occurring transmembrane domains. Small polypeptides that are provided according to the present invention which polypeptides maintain G-protein coupled receptor binding inhibition activity, are expected to have two

advantages over larger polypeptides. These advantages include (1) greater stability and diffusibility, and (2) less immunogenicity.

Since polypeptides according to the present invention are generally small (10-40, 20-30, 15-25, 30-45 amino acids), cell or tissue sources of G-protein coupled receptors are not required to practice the present invention, since known polypeptide syntheses steps can be used without undue experimentation to provide GPR polypeptides or sequences substantially corresponding thereto.

Pharmaceutical Preparations

Preparations of GPR polypeptides for parenteral administration include sterile aqueous or non-aqueous solutions, suspensions, and emulsions, which may contain auxiliary agents or excipients which are known in the art. Pharmaceutical compositions such as tablets and capsules can also be prepared according to routine methods.

By the term "protection" from infection or disease as used herein is intended "prevention," "suppression" or "treatment." "Prevention" involves administration of a GPR polypeptide, polypeptide derivative, or anti-idiotypic antibody prior to the induction of the disease.

"Suppression" involves administration of the composition prior to the clinical appearance of the disease.

"Treatment" involves administration of the protective composition after the appearance of the disease. It will be understood that in human and veterinary medicine, it is not always possible to distinguish between "preventing" and "suppressing" since the ultimate inductive event or events may be unknown, latent, or the patient is not ascertained until well after the occurrence of the event or events. Therefore, it is common to use the term "prophylaxis" as distinct from "treatment" to encompass both "preventing" and "suppressing" as defined herein. The term "protection," as used herein, is meant to include "prophylaxis."

At least one GPR polypeptide, antibody or anti-idiotypic antibody of the present invention may be administered by any means that achieve their intended purpose, for example, to treat GPR related pathologies, such as psychotic disorders, including schizophrenia, by inhibition of binding of Dopamine D_2 receptors

using a GPR polypeptide corresponding to a fragment or consensus portion of a dopamine D_2 transmembrane domain; in the form of a pharmaceutical composition.

For example, administration of such a composition may be by various parenteral routes such as subcutaneous, intravenous, intradermal, intramuscular, intraperitoneal, intranasal, transdermal, or buccal routes. Alternatively, or concurrently, administration may be by the oral route. Parenteral administration can be by bolus injection or by gradual perfusion over time.

A preferred mode of using a GPR pharmaceutical composition of the present invention is by intravenous or parenteral application.

A typical regimen for preventing, suppressing, or treating G-protein coupled receptor pathologies, such as dopamine receptor related schizophrenia, comprises administration of an effective amount of a GPR polypeptide, consensus sequence, or chemical derivative thereof, administered over a period of one or several days, up to and including between one week and about 24 months.

It is understood that the dosage of a GPR polypeptide of the present invention administered *in vivo* or *in vitro* will be dependent upon the age, sex, health, and weight of the recipient, kind of concurrent treatment, if any, frequency of treatment, and the nature of the effect desired. The ranges of effective doses provided below are not intended to limit the inventors and represent preferred dose ranges. However, the most preferred dosage will be tailored to the individual subject, as is understood and determinable by one of skill in the art, without undue experimentation.

The total dose required for each treatment may be administered by multiple doses or in a single dose. a GPR polypeptide or functional a chemical derivative thereof may be administered alone or in conjunction with other therapeutics directed to GPR related pathologies, such as a the dopamine receptor related pathology as a non limiting example, or directed to other symptoms of the disease.

Effective amounts of the a GPR polypeptide or composition, which may also include a functional derivative thereof, or a GPR anti-idiotypic antibody, are from about 0.01 μg to about 100 mg/kg body weight, and preferably from about 10 μg to about 50 mg/kg body

weight, such 0.05, 0.07, 0.09, 0.1, 0.5, 0.7, 0.9, 1, 2, 5, 10, 20, 25, 30, 40, 45, or 50 mg/kg.

Preparations for parenteral administration include sterile aqueous or non-aqueous solutions, suspensions, and emulsions, which may contain auxiliary agents or excipients which are known in the art. Pharmaceutical compositions such as tablets and capsules can also be prepared according to routine methods.

Pharmaceutical compositions comprising at least one GPR polypeptide of the present invention may include all compositions wherein the GPR polypeptide is contained in an amount effective to achieve its intended purpose. In addition to the GPR polypeptide, a pharmaceutical composition may contain suitable pharmaceutically acceptable carriers, such as comprising excipients and auxiliaries which facilitate processing of the active compounds into preparations which can be used pharmaceutically.

Pharmaceutical compositions include suitable solutions for administration intravenously, subcutaneously, dermally, orally, mucosally, rectally or may by injection or orally, and contain from about 0.01 to 99 percent, preferably from about 20 to 75 percent of active component (i.e. the antibody) together with the excipient. Pharmaceutical compositions for oral administration include tablets and capsules. Compositions which can be administered rectally include suppositories.

Example 1: Synthesis of a G-Protein Transmembrane Polypeptide and Consensus Polypeptide

The polypeptides in Figs. 1-5 were synthesized using the following procedure and include the following characteristics.

Peptide I (SEQ ID NO:1), as shown in Fig. 1, was used as a control for hydrophobic interaction alone as the mechanism of binding and was run in parallel with the test polypeptides described below. Polypeptide II (SEQ ID NO:2), as shown in Fig. 2, represents a membrane-spanning fragment of transmembrane segment III in the dopamine D_2 receptor. This particular fragment was chosen since it has been implicated in the β-adrenergic receptor as having many residues which are involved in ligand binding interaction.

Polypeptide III (SEQ ID NO:3), as shown in Fig. 3, represents the consensus polypeptide which was developed as a model for the dopamine D_2 system and polypeptide IV (SEQ ID NO:4), as shown in Fig. 4, is a control for length dependence to show how critical the polypeptide length is in binding studies. Polypeptide V (SEQ ID NO:5), as shown in Fig. 5, is a consensus sequence of transmembrane domains of dopamine receptors D_1 and D_2.

The above polypeptides I-V (SEQ ID NOS:1-5), as shown in Figs. 1-5, respectively, were synthesized using solid phase synthesis on a Milligen 9600 polypeptide synthesizer using Fmoc amino acids (provided by Milligen/Biosearch) and PAL polystyrene resin (Milligen/Biosearch). Coupling times were 1 hour and the polypeptides were cleaved by trifluoroacetic acid/phenol/H_2O/thioanisole/ethanedithiol (82.5:5:5:5:2.5) at room temperature for 2 hours. The filtrate was collected and washed with 2 mL of trifluoroacetic acid (TFA) and 1 mL of dichloromethane (DCM). The filtrate was reduced in vacuo to 2 ml in volume and the resulting polypeptide was precipitated out by the addition of water. The polypeptides were then dissolved in 1,1,1,3,3,3-hexafluoro-2-propanol [(HFIP) Eastman]; lyophilized; and stored at -20°C until purification. Polypeptides I-V (SEQ ID NOS:1-5), were purified using reverse-phase HPLC using a preparative Vydac C4 column (Vydac) at 60°C at a flow rate of 6.0 mL/min with a linear gradient of 0-100% B in a 60 min period at a UV detection wavelength of 275 nm.

Due to the highly hydrophobic nature of these polypeptides, methanol was used with 0.1% (W/V) TFA and 0.5% (W/V) HFIP as solvent A and 2-propanol with 0.1% TFA as solvent B, in order to purify these polypeptides. Further purification was performed with an analytical C4 column (Vydac) with an isocratic gradient of 40% B at a flow rate of 1 ml/min. Identity of the polypeptides was confirmed by Fast-atom bombardment mass spectrometry and electrospray mass spectrometry and amino acid analysis. Stock solutions of polypeptides were made in HFIP and stored at -20°- 80°C.

Circular Dichroism (CD). Spectra were recorded on an Aviv model 60 DS circular dichroism spectrophotometer at room temperature with a 1 cm by 1 mm cell. The amplitude of the CD signal was calibrated using 1 0.1% (w/v) solution of d (+)-camphorsulfonic acid

(Aldrich) and the wavelength of the CD signal was set using standard absorbance peaks of benzene vapor. Polypeptide concentrations were determined in a Cary 210 UV spectrophotomer with the absorbance measured at 280 nm. Helical content was estimated using CD signal intensity according to the method of Chen. et al Biochem. 13:3350-3359 (1974). This calculation compares the experimental ellipticity at 222 nm ([θ]222) ([θ]) to a theoretical [θ]222. The theoretical [θ]222 is empirically adjusted to account for differences in polypeptide length and is based on experimental CD data from a series of proteins with known crystal structures. Since both the curve shape and magnitude are important in analysis of a CD spectrum for secondary structure contributions, we also considered qualitatively the contributions to the spectral shapes from different secondary structures using reference curves for poly (L-lysine).

Fig. 6 shows a CD spectrum of the consensus polypeptide III (SEQ ID NO:3) demonstrating that the polypeptide III is only partially helical in a solvent system in which most membrane polypeptides are strongly helical.

Preparation of Small Unilamellar Vesicles. Polypeptides were incorporated into DMPC vesicles at lipid:peptide ratio of 147:1 in the following manner: polypeptide in HFIP was mixed with dimyrystyroyl- phosphatidylcholine (synthetic) (DMPC) in dry chloroform and dried to a film with a stream of dry nitrogen at 0°C. This residue was then dried further overnight under a vacuum (1×10^{-2} torr). The residue was then hydrated in 100 mM NaCl and sonicated for a 30-min period under nitrogen at 0°C. The suspension was sedimented for a 30-min at 100,000 g (4°C) to remove any residual titanium particles and large unilamellar vesicles. The supernatant was removed and sedimented once more at 159,000 g for a 45 min period at 4°C. The supernatant in the lower portion was used immediately. This basic procedure has been shown to reliably produce small unilamellar vesicles.

Radioligand Binding Assays. A 0.50 mL volume of 1.00 nM [^{3}H]-spiperone (New England specific activity 21.4 Ci/mmol) was added to assay tubes which contained 0.5 mL lipid/peptide supernatant, 0.5 mL Tris buffer pH 7.4 and 0.5 mL of cold drug for a final volume of 2.0 mL. Nonspecific binding was defined in the presence of 1 uM of

(+) butaclamol or 1 uM spiperone. Appropriate controls for lipid vesicles containing no polypeptide were also run. Assay tubes were prepared in triplicate and the mixture was incubated for 1 h at 25°C. Incubation was terminated by filtration through filters presoaked in 0.1% polyethyleneimine (w/v, Sigma) for at least 1 h prior to use.

Filters were then washed with 6.0 mL of cold 50 mM Tris-HCl buffer, pH 7.40. For detection of radioactivity, filters were placed in 2.0 mL of scintillation fluid (Scintiverse) and incubated for 24 h. The activity of the tritium was determined in a Beckman LS 7500 liquid scintillation counter. Specific binding of [^{3}H]-spiperone was defined as the difference in binding in the presence and absence of unlabeled (+) butaclamol.

Fig. 7 shows results of radioligand binding assays comparing polypeptide I (SEQ ID NO:1) as a control unit polypeptide III (SEQ ID NO:3) according to the present invention. Polypeptide III (SEQ ID NO:3) is shown to unexpectedly provide receptor-like functional binding, as demonstrated by binding to the neuroleptic agent, spiperone, into a stereoselective, concentration-dependent manner.

It has also been demonstrated that as little as 0.1% of a GPR polypeptide according to the present invention is able to form a receptor-like functional binding site. Thus, a GPR polypeptide of the present invention is unexpectedly shown to act both as GPR ligands and GPR binding sites.

All references cited herein, including journal articles or abstracts, published or corresponding U.S. or foreign patent applications, issued U.S. or foreign patents, or any other references, are entirely incorporated by reference herein, including all data, tables, figures, and text presented in the cited references. Additionally, the contents of the references cited within the references cited herein are also entirely incorporated by reference.

Reference to known method steps, conventional methods steps, known methods or conventional methods is not in any way an admission that any aspect, description or embodiment of the present invention is disclosed, taught or suggested in the relevant art.

The foregoing description of the specific embodiments will so fully reveal the general nature of the invention that others can, by applying knowledge within the skill of the art (including the contents of the references cited herein), readily modify and/or adapt for various applications such specific embodiments, without undue experimentation, without departing from the generic concept of the present invention. Therefore, such adaptations and modifications are intended to be comprehended within the meaning and range of equivalents of the disclosed embodiments, based on the teaching and guidance presented herein. It is to be understood that the phraseology or terminology herein is for the purpose of description and not of limitation, such that the terminology or phraseology of the present specification is to be interpreted by the skilled artisan in light of the teachings and guidance presented herein.

SEQUENCE LISTING

(1) GENERAL INFORMATION:

(i) APPLICANT: Murphy, Randall B.
Schuster, David I.

(ii) TITLE OF INVENTION: POLYPEPTIDES OF G-COUPLED RECEPTOR PROTEINS, AND COMPOSITIONS AND METHODS THEREOF

(iii) NUMBER OF SEQUENCES: 95

(iv) CORRESPONDENCE ADDRESS:
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(v) COMPUTER READABLE FORM:
(A) MEDIUM TYPE: Floppy disk
(B) COMPUTER: IBM PC compatible
(C) OPERATING SYSTEM: PC-DOS/MS-DOS
(D) SOFTWARE: PatentIn Release #1.0, Version #1.25

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(C) REFERENCE/DOCKET NUMBER: MURPHY=2

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(2) INFORMATION FOR SEQ ID NO:1:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 24 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:

Leu Ser Leu Leu Leu Ser Leu Leu Ser Leu Leu Leu Ser Leu Leu Ser
1 5 10 15

Leu Leu Leu Ser Leu Tyr Tyr Tyr
20

(2) INFORMATION FOR SEQ ID NO:2:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 27 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:

Asp Asp Ile Phe Val Thr Leu Asp Val Leu Phe Ser Thr Ala Ser Ile
1 5 10 15

Leu Asn Leu Ser Ala Ile Ser Leu Lys Lys Lys
20 25

(2) INFORMATION FOR SEQ ID NO:3:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 26 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:3:
Asp Tyr Ala Ile Phe Val Leu Tyr Ala Ser Ala Trp Leu Ser Phe Asn
1 5 10 15

Cys Pro Phe Ile Val Thr Leu Asn Ile Lys
20 25

(2) INFORMATION FOR SEQ ID NO:4:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 16 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:4:
Lys Ala Val Val Tyr Ser Ser Ile Val Ser Phe Tyr Val Phe Ile Asp
1 5 10 15

(2) INFORMATION FOR SEQ ID NO:5:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 27 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:5:
Asp Cys Asp Val Phe Val Phe Val Asp Ile Met Leu Cys Thr Ala Ser
1 5 10 15

Ile Phe Asn Leu Cys Ala Ile Ser Val Gly Lys
20 25

(2) INFORMATION FOR SEQ ID NO:6:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 317 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:6:
Ser Leu Val Leu Leu Leu Phe Ala Asp Phe Ser Ser Met Leu Gly Cys
1 5 10 15

Met Ala Val Leu Ile Gly Phe Trp Arg Leu Lys Leu Leu Arg Asn His
20 25 30

Val Thr Lys Val Ile Ala Cys Phe Cys Ala Thr Ser Phe Cys Lys Asp
35 40 45

Phe Pro Ser Thr Ile Leu Thr Leu Thr Asn Thr Ala Val Asn Gly Gly
50 55 60

Phe Pro Cys Tyr Leu Tyr Ala Ile Val Ile Thr Tyr Gly Ser Phe Ala
65 70 75 80

Cys Trp Leu Trp Thr Leu Ile Cys Leu Ala Ile Ser Ile Tyr Met Leu
85 90 95

Ile Val Lys Arg Glu Pro Glu Pro Glu Leu Phe Glu Lys Tyr Tyr Tyr
100 105 110

Leu Leu Cys Trp Gly Leu Pro Leu Ile Ser Thr Ile Gly Leu Lys Asn
115 120 125

Thr Val Gln Phe Val Gly Asn Trp Cys Trp Ile Gly Val Ser Phe Thr
130 135 140

Gly Tyr Arg Phe Gly Leu Phe Tyr Pro Phe Leu Phe Ile Trp Ala Ile
145 150 155 160

Ser Ala Val Leu Val Gly Leu Thr Ser Arg Tyr Thr Tyr Trp Ile His
165 170 175

Asn Gly Val Ser Asp Asn Lys Glu Lys His Leu Thr Tyr Gln Phe Lys
180 185 190

Leu Ile Asn Tyr Ile Ile Val Phe Leu Val Cys Trp Val Phe Ala Val
195 200 205

Val Asn Arg Ile Val Asn Gly Leu Asn Trp Pro Pro Ala Leu Asn Ile
210 215 220

Leu His Thr Tyr Leu Ser Val Ser His Gly Phe Trp Ala Ser Val Thr
225 230 235 240

Phe Ile Tyr Asn Asn Pro Leu Met Trp Arg Tyr Phe Gly Ala Lys Ile
245 250 255

Leu Thr Val Phe Thr Phe Phe Gly Tyr Phe Thr Asp Val Gln Lys Lys
260 265 270

Leu Glu Lys Asn Leu Ser Pro Tyr Ser Ser Ser Arg Gly Thr Ser Gly
275 280 285

Lys Thr Met Leu Gly His Pro Thr Gly Asp Asp Val Gln Cys Ser Ser
290 295 300

Asp Leu Gln Cys Ser Leu Glu Arg His Pro Asn Met Val
305 310 315

(2) INFORMATION FOR SEQ ID NO:7:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 349 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:7:
Val Tyr Ile Thr Val Glu Leu Ala Ile Ala Val Leu Ala Thr Leu Gly
1 5 10 15

Asn Val Leu Val Cys Trp Ala Val Trp Leu Asn Ser Asn Leu Asn Val
20 25 30

Thr Asn Tyr Phe Val Val Ser Leu Ala Ala Ala Asp Ile Ala Val Gly
35 40 45

Val Ile Ala Ile Pro Phe Ala Ile Thr Ile Ser Thr Gly Phe Cys Ala
50 55 60

Ala Cys His Asn Cys Leu Phe Phe Ala Cys Phe Val Leu Val Leu Thr

65 70 75 80

Gln Ser Ser Ile Phe Ser Leu Leu Ala Ile Ala Ile Asp Arg Tyr Ile
85 90 95

Ala Ile Arg Ile Pro Leu Arg Tyr Asn Gly Leu Val Thr Gly Thr Arg
100 105 110

Ala Lys Gly Ile Ile Ala Val Cys Trp Val Leu Ser Phe Ala Ile Gly
115 120 125

Leu Thr Pro Met Leu Gly Trp Asn Asn Cys Ser Gln Pro Lys Glu Gly
130 135 140

Arg Asn Tyr Ser Gln Gly Cys Gly Glu Gly Gln Val Ala Cys Leu Phe
145 150 155 160

Glu Asp Val Val Pro Met Asn Tyr Met Val Tyr Tyr Asn Phe Phe Ala
165 170 175

Phe Val Leu Val Pro Leu Leu Leu Val Tyr Leu Arg Ile Phe Leu Ala
180 185 190

Ala Arg Arg Gln Leu Lys Gln Met Glu Ser Gln Pro Leu Pro Gly Glu
195 200 205

Arg Ala Arg Ser Thr Leu Gln Lys Glu Val His Ala Ala Lys Ser Ala
210 215 220

Ile Ile Val Gly Leu Phe Ala Leu Cys Trp Leu Pro Leu His Ile Ile
225 230 235 240

Asn Cys Phe Thr Phe Phe Cys Pro Glu Cys Ser His Ala Pro Leu Trp
245 250 255

Leu Met Tyr Leu Thr Ile Val Leu Ser His Thr Asn Ser Trp Asn Pro
260 265 270

Phe Ile Tyr Ala Tyr Arg Ile Arg Glu Phe Arg Gln Thr Phe Arg Lys
275 280 285

Ile Ile Arg Ser His Val Leu Arg Arg Arg Glu Pro Phe Lys Ala Gly
290 295 300

Gly Thr Ser Ala Arg Ala Leu Ala Ala His Gly Ser Asp Gly Glu Gln
305 310 315 320

Ile Ser Leu Arg Leu Asn Gly His Pro Pro Gly Val Trp Ala Asn Gly
325 330 335

Ser Ala Pro His Pro Glu Arg Arg Pro Asn Gly Tyr Thr
340 345

(2) INFORMATION FOR SEQ ID NO:8:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 314 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:8:
Ala Tyr Ile Gly Ile Glu Val Leu Ile Ala Leu Val Ser Val Pro Gly
1 5 10 15

Trp Leu Val Ile Trp Ala Val Lys Val Asn Gln Ala Leu Arg Asp Ala
20 25 30

Thr Phe Cys Phe Ile Val Ser Ile Ala Val Ala Asp Val Ala Val Gly
35 40 45

Ala Leu Val Ile Pro Leu Ala Ile Leu Ile Asn Ile Gly Pro Arg Thr
50 55 60

Tyr Phe His Thr Cys Leu Met Val Ala Cys Pro Val Leu Ile Leu Thr
65 70 75 80

Gln Ser Ser Ile Ile Ala Leu Leu Ala Ile Ala Val Asp Arg Tyr Leu
85 90 95

Arg Val Lys Ile Pro Leu Arg Tyr Lys Thr Val Val Thr Pro Arg Arg
100 105 110

Ala Ala Val Ala Ile Ala Gly Cys Trp Ile Leu Ser Phe Val Val Gly
115 120 125

Leu Thr Pro Leu Phe Gly Trp Asn Arg Leu Gly Glu Ala Gln Arg Ala
130 135 140

Trp Ala Ala Asn Gly Ser Gly Gly Glu Pro Val Ile Lys Cys Glu Phe
145 150 155 160

Glu Lys Val Ile Ser Met Glu Tyr Met Val Tyr Phe Asn Phe Phe Val
165 170 175

Trp Val Leu Pro Pro Leu Leu Leu Met Val Leu Ile Tyr Leu Glu Val
180 185 190

Phe Tyr Leu Ile Arg Arg Gln Leu Gly Lys Lys Val Ser Ala Ser Ser
195 200 205

Gly Asp Pro Gln Lys Tyr Tyr Gly Lys Glu Leu Lys Ile Ala Lys Ser
210 215 220

Leu Ala Leu Ile Leu Phe Leu Phe Ala Leu Ser Trp Leu Pro Leu His
225 230 235 240

Ile Ile Asn Cys Ile Thr Leu Phe Cys Pro Ser Cys Arg Lys Pro Ser
245 250 255

Ile Leu Met Tyr Ile Ala Ile Phe Leu Thr His Gly Asn Ser Ala Met
260 265 270

Pro Ile Val Tyr Ala Phe Arg Ile Gln Lys Phe Arg Val Thr Phe Leu
275 280 285

Lys Ile Trp Asn Asp His Phe Arg Cys Gln Pro Thr Pro Pro Val Asp
290 295 300

Glu Asp Pro Pro Glu Glu Ala Pro His Asp
305 310

(2) INFORMATION FOR SEQ ID NO:9:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 342 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:9:
Val Ala Phe Ile Gly Ile Thr Thr Gly Leu Leu Ser Ile Ala Thr Val
1 5 10 15

Thr Gly Asn Leu Leu Val Leu Ile Ser Phe Lys Val Asn Thr Glu Leu

20 25 30

Lys Thr Val Asn Asn Tyr Phe Leu Leu Ser Ile Ala Cys Ala Asp Leu
35 40 45

Ile Ile Gly Thr Phe Ser Met Leu Tyr Leu Leu Met His Trp Ala Leu
50 55 60

Gly Thr Leu Ala Cys Asp Leu Trp Leu Ala Leu Asp Tyr Val Ala Ser
65 70 75 80

Asn Ala Ser Val Leu Asn Leu Leu Leu Ile Ser Phe Asp Arg Tyr Phe
85 90 95

Ser Val Thr Arg Pro Leu Ser Tyr Arg Ala Lys Arg Thr Pro Arg Arg
100 105 110

Ala Ala Ile Met Ile Gly Ile Ala Trp Leu Val Ser Phe Val Leu Trp
115 120 125

Ala Pro Ala Ile Leu Phe Trp Gln Tyr Leu Val Gly Glu Arg Thr Met
130 135 140

Leu Ala Gly Gln Cys Tyr Ile Gln Phe Leu Ser Gln Pro Ile Ile Thr
145 150 155 160

Phe Gly Thr Ala Met Ala Ala Phe Tyr Met Pro Val Thr Val Met Thr
165 170 175

Leu Tyr Trp Arg Ile Tyr Arg Phe Thr Glu Asn Arg Ala Arg Glu Leu
180 185 190

Gln Gly Ser Glu Thr Pro Gly Lys Gly Gly Gly Ser Ser Ser Ser Ser
195 200 205

Glu Arg Ser Gln Pro Gly Ala Glu Gly Ser Pro Glu Thr Pro Lys Gly
210 215 220

Gln Lys Pro Arg Gly Lys Glu Leu Ala Lys Arg Lys Thr Phe Ser Leu
225 230 235 240

Val Lys Glu Lys Lys Ala Ala Arg Thr Leu Ser Ala Ile Leu Leu Ala
245 250 255

Phe Ile Leu Thr Trp Thr Pro Tyr Asn Ile Met Val Leu Val Ser Thr
260 265 270

Phe Cys Lys Asp Cys Val Pro Glu Thr Leu Trp Glu Leu Gly Tyr Trp
275 280 285

Leu Ile Cys Tyr Val Asn Ser Thr Ile Asn Pro Trp Tyr Ala Leu Cys
290 295 300

Asn Lys Ala Phe Arg Asp Thr Phe Arg Leu Leu Leu Leu Cys Trp Asp
305 310 315 320

Lys Arg Arg Trp Arg Lys Ile Pro Lys Arg Pro Gly Ser Val His Arg
325 330 335

Thr Pro Ser Arg Gln Cys
340

(2) INFORMATION FOR SEQ ID NO:10:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 317 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single

(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:10:

Val Val Phe Ile Val Leu Val Ala Gly Ser Leu Ser Leu Val Thr Ile
1 5 10 15

Ile Gly Asn Ile Leu Val Met Val Ser Ile Lys Val Asn Arg His Tyr
20 25 30

Phe Leu Phe Ser Ile Ala Cys Ala Asp Leu Ile Ile Gly Val Phe Ser
35 40 45

Met Asn Leu Tyr Thr Leu Tyr Thr Val Ile Gly Tyr Trp Pro Leu Gly
50 55 60

Pro Val Val Cys Asp Leu Tyr Val Val Ser Asn Ala Ser Val Met Asn
65 70 75 80

Leu Leu Ile Ile Ser Phe Asp Arg Tyr Phe Cys Val Thr Lys Pro Leu
85 90 95

Thr Tyr Pro Val Lys Arg Thr Thr Lys Met Ala Gly Met Met Ile Ala
100 105 110

Ala Ala Trp Val Leu Ser Phe Ile Leu Trp Ala Pro Ala Ile Leu Phe
115 120 125

Trp Gln Phe Ile Val Gly Val Arg Thr Val Glu Asp Gly Glu Cys Tyr
130 135 140

Ile Gln Phe Phe Ser Asn Pro Ala Val Thr Phe Gly Thr Ala Ile Ala
145 150 155 160

Ala Phe Tyr Leu Pro Val Ile Ile Met Ile Val Leu Tyr Trp His Ile
165 170 175

Ser Arg Ala Ser Lys Ser Arg Ile Lys Lys Asp Lys Lys Glu Pro Val
180 185 190

Ala Asn Gln Asp Pro Val Ser Pro Ser Leu Val Gln Gly Arg Ile Val
195 200 205

Lys Pro Leu Ser Ser Asp Asp Lys Ile Val Arg Arg Thr Lys Gln Pro
210 215 220

Ala Lys Lys Lys Pro Pro Pro Ser Arg Glu Lys Lys Val Thr Arg Thr
225 230 235 240

Ile Ala Ile Leu Leu Ala Phe Ile Ile Thr Trp Ala Pro Tyr Asn Val
245 250 255

Met Val Leu Ile Asn Thr Phe Cys Ala Pro Cys Ile Pro Asn Thr Val
260 265 270

Trp Arg Ile Gly Tyr Trp Leu Cys Tyr Ile Asn Ser Thr Ile Asn Pro
275 280 285

Ala Cys Tyr Ala Leu Cys Asn Ala Thr Phe Lys Lys Thr Phe Lys His
290 295 300

Leu Ile Met Cys His Tyr Lys Asn Ile Gly Ala Thr Arg
305 310 315

(2) INFORMATION FOR SEQ ID NO:11:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 355 amino acids

(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:11:

Trp Phe Ile Ala Phe Leu Thr Gly Ile Leu Ala Leu Val Thr Ile Ile
1 5 10 15

Gly Asn Ile Leu Val Ile Val Ser Phe Lys Val Asn Lys Gln Leu Lys
20 25 30

Thr Val Asn Asn Tyr Phe Leu Leu Ser Leu Ala Cys Ala Asp Leu Ile
35 40 45

Ile Gly Val Ile Ser Met Asn Leu Phe Thr Thr Tyr Ile Ile Met Asn
50 55 60

Arg Trp Ala Leu Gly Asn Thr Ala Cys Asp Leu Trp Ile Ala Ile Asp
65 70 75 80

Tyr Val Ala Ser Asn Ala Ser Val Leu Asn Leu Leu Val Ile Ser Phe
85 90 95

Asp Arg Tyr Phe Ser Ile Thr Arg Pro Leu Thr Tyr Arg Ala Lys Arg
100 105 110

Thr Thr Lys Arg Ala Gly Val Met Ile Gly Leu Ala Trp Val Ile Ser
115 120 125

Phe Val Leu Trp Ala Pro Ala Ile Leu Phe Trp Gln Tyr Phe Val Gly
130 135 140

Lys Arg Thr Val Pro Pro Gly Glu Cys Phe Ile Gln Phe Leu Ser Glu
145 150 155 160

Pro Thr Ile Thr Phe Gly Thr Ala Ile Ala Ala Phe Tyr Met Pro Val
165 170 175

Thr Ile Met Arg Ile Leu Tyr Trp Arg Ile Tyr Lys Glu Thr Glu Lys
180 185 190

Arg Thr Lys Glu Leu Ala Gly Leu Gln Ala Ser Gly Thr Glu Ala Glu
195 200 205

Thr Glu Asn Phe Val His Pro Thr Gly Ser Ser Arg Ser Cys Ser Ser
210 215 220

Tyr Glu Leu Gln Gln Gln Lys Arg Phe Ala Leu Lys Thr Arg Ser Gln
225 230 235 240

Ile Thr Lys Arg Lys Leu Leu Val Lys Glu Lys Lys Ala Ala Gln Thr
245 250 255

Leu Ser Ala Ile Leu Leu Ala Phe Ile Ile Thr Trp Thr Pro Tyr Asn
260 265 270

Ile Met Val Leu Val Asn Thr Phe Cys Asp Ser Cys Ile Pro Lys Thr
275 280 285

Tyr Trp Asn Leu Gly Gly Tyr Trp Leu Cys Tyr Ile Asn Ser Thr Val
290 295 300

Asn Pro Val Cys Tyr Ala Leu Cys Asn Lys Thr Phe Arg Thr Thr Phe
305 310 315 320

Lys Thr Leu Leu Leu Cys Gln Cys Asp Lys Arg Lys Arg Arg Lys Gln

325 330 335

Gln Tyr Gln Gln Arg Gln Ser Val Ile Phe His Lys Arg Val Pro Glu
340 345 350

Gln Ala Leu
355

(2) INFORMATION FOR SEQ ID NO:12:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 333 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:12:

Met Val Phe Ile Ala Thr Val Arg Gly Ser Leu Ser Leu Val Thr Val
1 5 10 15

Val Gly Asn Ile Leu Val Met Leu Ser Ile Lys Val Asn Arg Gln Leu
20 25 30

Gln Thr Val Asn Asn Tyr Phe Leu Phe Ser Ile Ala Cys Ala Asp Leu
35 40 45

Ile Ile Gly Ala Phe Ser Met Asn Leu Tyr Thr Val Tyr Ile Ile Lys
50 55 60

Gly Tyr Trp Pro Leu Gly Ala Trp Cys Asp Leu Trp Leu Ala Leu Asp
65 70 75 80

Tyr Val Val Ser Asn Ala Ser Val Met Leu Leu Ile Ile Ser Phe Asp
85 90 95

Arg Tyr Phe Cys Val Thr Lys Pro Leu Thr Tyr Pro Ala Arg Arg Thr
100 105 110

Thr Lys Met Ala Gly Ile Met Ile Ala Ala Ala Trp Val Leu Ser Phe
115 120 125

Val Leu Trp Ala Pro Ala Ile Leu Phe Trp Gln Phe Val Val Gly Lys
130 135 140

Arg Thr Val Pro Asp Asn Gln Cys Phe Ile Gln Phe Leu Ser Asn Pro
145 150 155 160

Ala Val Thr Phe Gly Thr Ala Ile Ala Ala Phe Tyr Leu Pro Val Val
165 170 175

Ile Met Ile Val Leu Tyr Ile His Ile Ser Leu Ala Ser Arg Ser Arg
180 185 190

Val His Lys His Arg Pro Glu Gly Pro Lys Glu Lys Lys Ala Lys Thr
195 200 205

Ile Ala Phe Leu Lys Ser Pro Ile Met Gln Ser Val Lys Lys Pro Pro
210 215 220

Pro Gly Glu Ala Lys Phe Ala Ser Ile Ala Arg Asn Gln Val Arg Lys
225 230 235 240

Lys Arg Gln Leu Ala Ala Arg Glu Arg Lys Val Thr Arg Thr Ile Phe
245 250 255

Ala Ile Leu Leu Ala Phe Ile Leu Thr Trp Thr Pro Tyr Asn Val Met
260 265 270

Val Leu Val Asn Thr Phe Cys Gln Ser Cys Ile Pro Asp Thr Val Trp
275 280 285

Ser Ile Gly Tyr Trp Leu Ile Cys Tyr Val Asn Ser Thr Ile Asn Pro
290 295 300

Ala Cys Tyr Ala Leu Cys Asn Ala Thr Phe Lys Lys Thr Phe Arg His
305 310 315 320

Leu Leu Leu Cys Gln Arg Tyr Asn Ile Gly Thr Ala Arg
325 330

(2) INFORMATION FOR SEQ ID NO:13:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 348 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:13:
Val Ile Thr Ile Ala Val Val Thr Ala Val Val Ser Leu Met Thr Ile
1 5 10 15

Val Gly Asn Val Leu Val Met Ile Ser Phe Lys Val Asn Ser Gln Leu
20 25 30

Lys Thr Val Asn Asn Tyr Tyr Leu Leu Ser Ile Ala Cys Ala Asp Leu
35 40 45

Ile Ile Gly Ile Phe Ser Met Asn Leu Tyr Thr Thr Tyr Ile Leu Ile
50 55 60

Met Gly Arg Trp Ala Leu Gly Ser Leu Ala Cys Asp Leu Trp Leu Ala
65 70 75 80

Ile Asp Tyr Val Ala Ser Asn Ala Ser Val Leu Asn Leu Leu Val Ile
85 90 95

Ser Phe Asp Arg Tyr Phe Ser Ile Thr Arg Pro Leu Thr Tyr Arg Ala
100 105 110

Lys Arg Thr Pro Lys Arg Ala Gly Ile Met Ile Gly Ile Ala Trp Leu
115 120 125

Ile Ser Phe Ile Leu Trp Ala Pro Ala Ile Leu Cys Trp Gln Tyr Leu
130 135 140

Val Gly Lys Arg Thr Val Pro Ile Asp Glu Cys Gln Ile Gln Phe Leu
145 150 155 160

Ser Glu Pro Thr Ile Thr Phe Gly Thr Ala Ile Ala Ala Phe Tyr Ile
165 170 175

Pro Val Ser Ile Met Arg Ile Leu Tyr Cys Arg Ile Tyr Arg Glu Thr
180 185 190

Glu Lys Arg Thr Lys Asp Leu Ala Asp Leu Gln Gly Ser Asp Ser Val
195 200 205

Tyr Lys Ala Glu Lys Arg Lys Pro Ala His Arg Ala Leu Phe Arg Ser
210 215 220

Cys Leu Arg Cys Pro Arg Pro Thr Lys Gly Leu Asn Pro Asn Pro Ser
225 230 235 240

His Gln Met Thr Lys Arg Lys Arg Met Ser Leu Val Lys Glu Arg Lys

245 250 255

Ala Ala Gln Thr Leu Ser Ala Ile Leu Leu Ala Phe Ile Ile Thr Trp
260 265 270

Thr Pro Tyr Asn Ile Met Val Leu Val Ser Thr Phe Cys Asp Lys Cys
275 280 285

Val Pro Val Thr Leu Trp His Leu Gly Tyr Trp Leu Cys Tyr Ile Asn
290 295 300

Ser Thr Val Asn Pro Ile Cys Tyr Ala Leu Cys Asn Arg Thr Phe Arg
305 310 315 320

Lys Thr Phe Ile Met Leu Leu Cys Arg Trp Lys Lys Lys Lys Val Glu
325 330 335

Glu Lys Leu Tyr Trp Gln Gly Asn Ser Lys Leu Pro
340 345

(2) INFORMATION FOR SEQ ID NO:14:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 377 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:14:
Thr Ala Gly Asp Cys Leu Ile Met Leu Ile Val Leu Leu Ile Val Ala
1 5 10 15

Gly Asn Val Leu Val Ile Val Ala Ile Ala Lys Thr Pro Arg Leu Gln
20 25 30

Thr Leu Thr Asn Leu Phe Ile Met Ser Ile Ala Ser Ala Asp Leu Val
35 40 45

Met Leu Leu Leu Val Val Pro Phe Cys Ala Thr Leu Val Val Trp Gly
50 55 60

Arg Trp Glu Tyr Gly Ser Phe Phe Cys Glu Leu Trp Thr Ser Val Asp
65 70 75 80

Val Leu Cys Val Thr Ala Ser Ile Glu Thr Leu Cys Val Ile Ala Leu
85 90 95

Asp Arg Tyr Leu Ala Ile Thr Ser Pro Phe Arg Tyr Gln Ser Leu Leu
100 105 110

Thr Arg Ala Arg Ala Arg Gly Leu Val Cys Thr Val Trp Ala Ile Ser
115 120 125

Ala Leu Val Ser Phe Leu Pro Ile Leu Leu Ser Asp Glu Ala Arg Arg
130 135 140

Cys Tyr Asn Asp Pro Lys Cys Cys Asp Phe Val Thr Asn Arg Ala Tyr
145 150 155 160

Ala Ile Ala Ser Ser Val Val Ser Phe Tyr Val Pro Leu Cys Ile Met
165 170 175

Phe Val Tyr Leu Arg Val Phe Arg Glu Ala Gln Lys Gln Val Lys Lys
180 185 190

Ile Asp Ser Cys Glu Arg Arg Phe Leu Gly Gly Pro Ala Arg Pro Pro
195 200 205

Ser Pro Ser Pro Ser Pro Val Pro Ala Pro Ala Pro Pro Gly Pro Pro
210 215 220

Arg Pro Ala Ala Ala Ala Ala Thr Ala Pro Leu Ala Asn Gly Arg Ala
225 230 235 240

Gly Lys Arg Arg Pro Ser Arg Leu Val Ala Leu Arg Glu Gln Lys Ala
245 250 255

Leu Lys Thr Leu Gly Ile Ile Met Gly Val Phe Thr Leu Cys Trp Leu
260 265 270

Pro Phe Phe His Arg Glu Leu Val Pro Asp Arg Leu Phe Val Phe Phe
275 280 285

Asn Trp Leu Arg Tyr Ala Asn Ser Ala Phe Asn Pro Ile Ile Tyr Cys
290 295 300

Arg Ser Pro Asp Phe Arg Lys Ala Phe Gln Gly Leu Leu Cys Cys Ala
305 310 315 320

Arg Arg Ala Ala Arg Arg Arg His Ala Thr His Gly Asp Arg Pro Arg
325 330 335

Ala Ser Gly Cys Ile Ala Arg Pro Gly Pro Pro Ser Pro Gly Ala Ala
340 345 350

Ser Asp Asp Asp Asp Asp Asp Val Val Gly Ala Thr Pro Pro Ala Arg
355 360 365

Leu Leu Glu Pro Trp Ala Gly Cys Asn
370 375

(2) INFORMATION FOR SEQ ID NO:15:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 362 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:15:
Val Val Gly Ile Val Met Ser Leu Ile Val Leu Ala Ile Val Phe Gly
1 5 10 15

Asn Val Leu Val Ile Thr Ala Ile Ala Lys Phe Glu Arg Leu Gln Thr
20 25 30

Val Thr Asn Tyr Phe Ile Thr Ser Ile Ala Cys Ala Asp Leu Val Met
35 40 45

Gly Leu Ala Val Val Pro Phe Gly Ala Ala His Ile Leu Met Lys Met
50 55 60

Trp Thr Phe Gly Asn Phe Trp Cys Glu Phe Trp Thr Ser Ile Asp Val
65 70 75 80

Leu Cys Val Thr Ala Ser Ile Glu Thr Leu Cys Val Ile Ala Val Asp
85 90 95

Arg Tyr Phe Ala Ile Thr Ser Pro Phe Lys Tyr Gln Ser Leu Leu Thr
100 105 110

Lys Asn Lys Ala Arg Val Ile Ile Ile Met Val Trp Ile Val Ser Gly
115 120 125

Leu Thr Ser Phe Leu Pro Ile Leu Tyr Arg Ala Thr His Gln Glu Ala

130 135 140

Ile Asn Cys Tyr Ala Asn Glu Thr Cys Cys Asp Phe Phe Thr Asn Gln
145 150 155 160

Ala Tyr Ala Ala Ser Ser Ala Val Ser Phe Tyr Val Pro Leu Val Ile
165 170 175

Met Val Phe Val Tyr Ser Arg Val Phe Gln Glu Ala Lys Arg Gln Leu
180 185 190

Gln Lys Ile Asp Lys Ser Glu Gly Arg Phe Ile Phe Val Gln Asn Leu
195 200 205

Ser Gln Val Glu Gln Asp Gly Arg Thr Gly His Gly Leu Arg Arg Ser
210 215 220

Ser Lys Phe Cys Leu Lys Glu His Lys Ala Leu Lys Thr Leu Gly Ile
225 230 235 240

Ile Pro Cys Thr Phe Thr Leu Cys Trp Leu Pro Phe Phe Ile Val Asn
245 250 255

Ile Val Val Ile Gln Asp Asn Leu Ile Arg Lys Glu Val Tyr Ile Leu
260 265 270

Leu Asn Trp Ile Gly Tyr Val Asn Ser Gly Phe Asn Pro Leu Ile Tyr
275 280 285

Cys Arg Ser Pro Asp Phe Arg Ile Ala Phe Gln Glu Leu Leu Cys Leu
290 295 300

Arg Arg Ser Ser Leu Lys Ala Tyr Gly Asn Gly Tyr Ser Ser Asn Gly
305 310 315 320

Asn Thr Gly Glu Gln Ser Gly Tyr His Val Glu Gln Glu Lys Glu Asn
325 330 335

Lys Leu Leu Cys Glu Asp Leu Pro Gly Thr Glu Asp Phe Val Gly His
340 345 350

Gln Gly Thr Val Pro Ser Asp Asn Ile Asp
355 360

(2) INFORMATION FOR SEQ ID NO:16:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 362 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:16:
Ala Ala Leu Ala Gly Ala Leu Leu Ala Leu Ala Val Leu Ala Thr Val
1 5 10 15

Gly Gly Asn Leu Leu Val Ile Val Ala Ile Ala Trp Thr Pro Arg Leu
20 25 30

Gln Thr Met Thr Asn Val Phe Val Thr Ser Leu Ala Ala Ala Asp Leu
35 40 45

Asp Leu Leu Val Val Pro Pro Ala Ala Thr Leu Ala Leu Thr Gly His
50 55 60

Trp Pro Leu Gly Ala Thr Gly Cys Glu Leu Trp Thr Ser Val Asp Val
65 70 75 80

Leu Cys Val Thr Ala Ser Ile Glu Thr Leu Cys Ala Ile Ala Val Asp
85 90 95

Arg Tyr Leu Ala Val Thr Asn Pro Leu Arg Tyr Gly Ala Leu Val Thr
100 105 110

Lys Arg Cys Ala Arg Thr Ala Trp Leu Val Trp Val Val Ser Ala Ala
115 120 125

Val Ser Phe Ala Pro Ile Met Ser Gln Trp Trp Arg Val Gly Ala Asp
130 135 140

Ala Glu Ala Gln Arg Cys His Ser Asn Pro Arg Cys Cys Ala Phe Ala
145 150 155 160

Ser Asn Met Pro Tyr Ala Val Leu Leu Ser Ser Ser Val Ser Phe Tyr
165 170 175

Leu Pro Leu Leu Leu Phe Val Tyr Ala Arg Val Phe Trp Ala Thr Arg
180 185 190

Gln Leu Arg Leu Leu Arg Gly Glu Leu Gly Arg Phe Pro Pro Glu Glu
195 200 205

Ser Pro Pro Ala Pro Ser Arg Ser Leu Ala Pro Ala Pro Val Gly Thr
210 215 220

Gly Ala Pro Pro Glu Gly Val Pro Ala Cys Gly Arg Pro Pro Ala Arg
225 230 235 240

Leu Ile Pro Ile Arg Glu His Arg Ala Leu Cys Thr Leu Gly Leu Ile
245 250 255

Met Gly Thr Phe Thr Leu Cys Trp Leu Pro Phe Phe Ile Ala Asn Val
260 265 270

Leu Arg Ala Leu Gly Gly Pro Ser Leu Val Pro Gly Pro Ala Phe Leu
275 280 285

Ala Leu Asn Trp Leu Ile Gly Tyr Ala Asn Ser Ala Phe Asn Pro Leu
290 295 300

Ile Tyr Cys Arg Ser Pro Asp Phe Arg Ser Ala Phe Arg Arg Leu Leu
305 310 315 320

Cys Arg Cys Gly Arg Arg Leu Pro Pro Glu Pro Cys Ala Ala Ala Arg
325 330 335

Pro Ala Leu Phe Pro Ser Gly Val Pro Ala Ala Glu Ser Ser Pro Ala
340 345 350

Gln Pro Arg Leu Cys Gln Arg Leu Asp Gly
355 360

(2) INFORMATION FOR SEQ ID NO:17:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 375 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:17:
Ala Ile Leu Leu Gly Val Ile Leu Gly Gly Leu Ile Leu Phe Gly Val
1 5 10 15

Leu Gly Asn Ile Leu Val Ile Leu Ser Val Ala Cys His Arg His Leu

20 25 30

His Ser Val Thr His Tyr Tyr Ile Val Asn Leu Ala Val Ala Asp Leu
35 40 45

Leu Leu Thr Ser Thr Val Leu Pro Phe Ser Ala Ile Phe Glu Ile Leu
50 55 60

Gly Tyr Trp Lys Phe Gly Arg Val Phe Cys Asn Val Trp Ala Ala Val
65 70 75 80

Asp Val Leu Cys Cys Thr Ala Ser Ile Met Leu Leu Cys Ile Ile Ser
85 90 95

Ile Asp Arg Tyr Ile Gly Val Ser Tyr Pro Leu Arg Tyr Pro Thr Ile
100 105 110

Val Thr Gln Lys Arg Gly Leu Met Ala Leu Leu Cys Val Trp Ala Leu
115 120 125

Ser Leu Val Ile Ser Ile Gly Pro Leu Phe Gly Trp Arg Gln Pro Ala
130 135 140

Pro Glu Asp Glu Thr Ile Cys Gln Ile Asn Glu Glu Pro Gly Tyr Val
145 150 155 160

Leu Phe Ser Ala Leu Gly Ser Phe Tyr Val Pro Leu Thr Ile Ile Leu
165 170 175

Val Met Tyr Cys Arg Val Tyr Val Val Ala Lys Arg Glu Ser Arg Gly
180 185 19?

Leu Lys Ser Gly Leu Lys Thr Asp Lys Ser Asp Ser Glu Gln Val Thr
195 200 205

Leu Arg Ile His Arg Lys Asn Ala Gln Val Gly Gly Ser Gly Val Thr
210 215 220

Ser Ala Lys Asn Lys Thr His Phe Ser Val Arg Leu Leu Lys Phe Ser
225 230 235 240

Arg Glu Lys Lys Ala Ala Lys Thr Leu Gly Ile Val Val Gly Cys Phe
245 250 255

Val Leu Cys Trp Leu Pro Phe Phe Leu Val Met Pro Ile Gly Ser Phe
260 265 270

Phe Pro Asp Phe Arg Pro Ser Glu Thr Val Phe Lys Ile Ala Phe Trp
275 280 285

Leu Gly Tyr Ile Asn Ser Cys Ile Asn Pro Ile Ile Tyr Pro Cys Ser
290 295 300

Ser Gln Glu Phe Lys Lys Ala Phe Gln Asn Val Leu Arg Ile Gln Cys
305 310 315 320

Leu Arg Arg Lys Gln Ser Ser Lys His Thr Leu Gly Tyr Thr Leu His
325 330 335

Ala Pro Ser His Val Leu Glu Gly Gln His Lys Asp Leu Val Arg Ile
340 345 350

Pro Val Gly Ser Ala Glu Thr Phe Tyr Lys Ile Ser Lys Thr Asp Gly
355 360 365

Val Cys Glu Trp Lys Ile Phe
370 375

(2) INFORMATION FOR SEQ ID NO:18:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 370 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:18:

```
Ala Ile Ser Val Gly Leu Val Leu Gly Ala Phe Ile Leu Phe Ala Ile
1               5                  10                  15

Val Gly Asn Ile Leu Val Ile Leu Ser Val Ala Cys Asn Arg His Leu
            20                  25                  30

Arg Thr Pro Thr Asn Tyr Phe Ile Val Asn Ile Ala Ile Ala Asp Leu
        35                  40                  45

Leu Leu Ser Phe Thr Val Leu Pro Phe Ser Ala Thr Leu Glu Val Leu
    50                  55                  60

Gly Tyr Trp Val Leu Gly Arg Ile Phe Cys Asp Ile Trp Ala Ala Val
65                  70                  75                  80

Asp Val Leu Cys Cys Thr Ala Ser Ile Leu Ser Leu Cys Ala Ile Ser
                85                  90                  95

Ile Asp Arg Tyr Ile Gly Val Arg Tyr Ser Leu Gln Tyr Pro Thr Leu
            100                 105                 110

Val Thr Arg Arg Tyr Ala Ile Ile Ala Leu Leu Ser Val Trp Val Leu
        115                 120                 125

Ser Thr Val Ile Ser Ile Gly Pro Leu Leu Gly Trp Lys Glu Pro Ala
    130                 135                 140

Pro Asn Asp Asp Lys Glu Cys Val Thr Glu Glu Pro Phe Leu Phe Cys
145                 150                 155                 160

Ser Leu Gly Ser Phe Tyr Ile Pro Ile Ala Val Ile Leu Val Met Tyr
                165                 170                 175

Cys Arg Val Tyr Ile Val Ala Lys Arg Thr Thr Lys Asn Leu Glu Ala
            180                 185                 190

Gly Val Met Lys Glu Met Ser Asn Ser Lys Phe Leu Thr Leu Arg Ile
        195                 200                 205

His Trp Ser Lys Asn Phe His Glu Asp Thr Leu Ser Ser Thr Lys Ala
    210                 215                 220

Lys Gly His Asn Pro Arg Ser Ser Ile Ala Val Lys Leu Phe Lys Phe
225                 230                 235                 240

Ser Arg Glu Lys Lys Ala Ala Lys Thr Leu Gly Ile Val Val Gly Trp
                245                 250                 255

Ile Leu Cys Trp Leu Pro Phe Phe Ile Ala Leu Pro Leu Gly Ser Leu
            260                 265                 270

Phe Ser Thr Leu Lys Pro Pro Asp Ala Val Phe Lys Trp Phe Trp Leu
        275                 280                 285

Gly Tyr Phe Asn Ser Cys Leu Asn Pro Ile Ile Tyr Pro Cys Ser Ser
    290                 295                 300

Lys Glu Phe Lys Arg Ala Leu Leu Gly Cys Gln Cys Arg Gly Gly Arg
```

305 310 315 320

Arg Arg Arg Arg Arg Arg Arg Leu Ala Cys Ala Tyr Thr Tyr Arg Pro
325 330 335

Trp Thr Arg Gly Gly Ser Leu Glu Arg Ser Gln Ser Arg Lys Asp Ser
340 345 350

Ile Asp Asp Ser Gly Ser Cys Met Ser Gly Gln Lys Arg Thr Leu Pro
355 360 365

Ser Ala
370

(2) INFORMATION FOR SEQ ID NO:19:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 330 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:19:
Val Ala Gly Leu Ala Ala Val Val Gly Phe Leu Ile Val Phe Thr Val
1 5 10 15
Val Gly Asn Val Leu Val Val Ile Ala Val Leu Thr Ser Arg Ala Leu
20 25 30
Arg Ala Pro Gln Asn Leu Phe Leu Val Ser Ile Ala Ser Ala Asp Ile
35 40 45

Leu Val Ala Thr Leu Val Met Pro Phe Ser Leu Ala Asn Glu Ile Met
50 55 60

Tyr Trp Tyr Phe Gly Gln Val Trp Cys Gly Val Tyr Leu Ala Ile Asp
65 70 75 80

Val Leu Phe Cys Thr Ser Ser Ile Val His Leu Cys Ala Ile Ser Leu
85 90 95

Asp Arg Tyr Trp Ser Val Thr Gln Ala Val Glu Tyr Asn Leu Lys Arg
100 105 110

Thr Pro Arg Arg Val Lys Ala Thr Ile Val Ala Val Trp Leu Ile Ser
115 120 125

Ala Val Ile Ser Phe Pro Pro Leu Val Ser Leu Tyr Arg Gln Pro Asp
130 135 140

Gly Ala Ala Tyr Pro Gln Cys Gly Leu Asn Asp Glu Thr Trp Tyr Ile
145 150 155 160

Leu Ser Ser Cys Ile Gly Ser Phe Phe Ala Pro Cys Leu Ile Tyr Leu
165 170 175

Leu Val Tyr Ala Arg Ile Tyr Arg Val Ala Lys Arg Arg Thr Arg Thr
180 185 190

Leu Ser Glu Lys Arg Ala Pro Val Gly Pro Asp Gly Ala Ser Pro Thr
195 200 205

Thr Glu Asn Gly Leu Gly Ala Ala Ala Gly Glu Ala Arg Thr Gly Thr
210 215 220

Ala Arg Phe Leu Ser Arg Arg Arg Arg Ala Arg Ser Ser Val Cys Arg
225 230 235 240

Arg Lys Val Ala Gln Ala Arg Glu Lys Arg Phe Thr Phe Val Leu Ala

```
                    245                 250                 255

Leu Val Phe Val Leu Cys Trp Phe Pro Phe Phe Phe Ile Tyr Ser Leu
            260                 265                 270

Tyr Gly Ile Cys Arg Glu Ala Cys Gln Val Pro Gly Pro Leu Phe Lys
        275                 280                 285

Phe Phe Phe Trp Ile Gly Tyr Cys Asn Ser Ser Leu Asn Pro Val Ile
    290                 295                 300

Tyr Thr Val Phe Asn Gln Asp Phe Arg Pro Ser Phe Lys His Ile Leu
305                 310                 315                 320

Phe Arg Arg Arg Arg Arg Gly Phe Arg Gln
                    325                 330
```

(2) INFORMATION FOR SEQ ID NO:20:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 330 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:20:

```
Thr Ala Ala Ile Ala Ala Ala Ile Thr Phe Leu Ile Leu Phe Thr Ile
1                   5                   10                  15

Phe Gly Asn Ala Leu Val Ile Ile Ala Val Leu Thr Ser Arg Ser Leu
            20                  25                  30

Arg Ala Pro Gln Asn Leu Phe Leu Val Ser Ile Ala Ala Ala Asp Ile
        35                  40                  45

Leu Val Ala Thr Leu Ile Ile Pro Phe Ser Leu Ala Asn Glu Leu Leu
    50                  55                  60

Gly Tyr Trp Tyr Phe Arg Arg Thr Trp Cys Glu Val Tyr Leu Ala Leu
65                  70                  75                  80

Asp Val Leu Phe Cys Thr Ser Ser Ile Val His Leu Cys Ala Ile Ser
                85                  90                  95

Leu Asp Arg Tyr Trp Ala Val Ser Arg Ala Leu Glu Tyr Asn Ser Lys
            100                 105                 110

Arg Thr Pro Arg Arg Ile Lys Cys Ile Ile Leu Thr Val Trp Leu Ile
        115                 120                 125

Ala Ala Val Ile Ser Leu Pro Pro Leu Ile Tyr Lys Gly Asp Gln Gly
    130                 135                 140

Pro Gln Pro Arg Gly Arg Pro Gln Cys Lys Leu Asn Gln Glu Ala Trp
145                 150                 155                 160

Tyr Ile Leu Ser Ser Ile Gly Ser Phe Phe Ala Pro Cys Leu Ile Leu
                165                 170                 175

Leu Val Tyr Leu Arg Ile Tyr Leu Ile Ala Lys Arg Ser Asn Arg Arg
            180                 185                 190

Gly Pro Arg Ala Lys Cys Gly Pro Gly Gln Gly Glu Ser Lys Gln Pro
        195                 200                 205

Arg Pro Asp His Gly Gly Ala Ile Ala Ser Ala Lys Leu Pro Ala Ile
```

210 215 220

Ala Ser Gly Arg Gly Val Gly Ala Ile Gly Gly Gln Trp Trp Arg Arg
225 230 235 240

Arg Ala His Val Thr Arg Glu Lys Arg Phe Thr Phe Val Leu Ala Val
245 250 255

Val Ile Gly Val Phe Val Leu Cys Trp Phe Pro Phe Phe Phe Ser Tyr
260 265 270

Ser Leu Gly Ala Ile Cys Pro Lys His Cys Lys Val Pro His Gly Leu
275 280 285

Phe Gln Phe Phe Phe Trp Ile Gly Tyr Cys Asn Ser Ser Leu Asn Pro
290 295 300

Val Ile Tyr Thr Ile Phe Asn Gln Asp Phe Arg Met Phe Arg Arg Ile
305 310 315 320

Leu Cys Arg Pro Trp Thr Gln Thr Ala Trp
325 330

(2) INFORMATION FOR SEQ ID NO:21:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 330 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:21:
Thr Leu Thr Leu Val Cys Ile Ala Cys Leu Ser Leu Thr Val Phe Gly
1 5 10 15

Asn Val Leu Val Ile Ile Ala Val Phe Thr Ser Arg Ala Leu Lys Ala
20 25 30

Pro Gln Asn Leu Phe Leu Val Ser Ile Ala Ser Ala Asp Ile Leu Val
35 40 45

Ala Thr Leu Val Ile Pro Phe Ser Leu Ala Asn Glu Val Asn Gly Tyr
50 55 60

Trp Tyr Phe Gly Lys Trp Cys Glu Ile Tyr Leu Ala Leu Asp Val Leu
65 70 75 80

Phe Cys Thr Ser Ser Ile Val His Leu Cys Ala Ile Ser Leu Asp Arg
85 90 95

Tyr Trp Ser Ile Thr Gln Ala Ile Glu Tyr Asn Leu Lys Arg Thr Pro
100 105 110

Arg Arg Ile Lys Ala Ile Ile Ile Thr Val Trp Val Ile Ser Ala Val
115 120 125

Ile Ser Phe Pro Pro Leu Ile Ser Ile Glu Lys Lys Gly Gly Gly Gly
130 135 140

Gly Pro Gln Pro Ala Glu Pro Arg Cys Glu Ile Asn Asp Gln Lys Trp
145 150 155 160

Tyr Val Ile Ser Ser Cys Ile Gly Ser Phe Phe Ala Pro Cys Leu Ile
165 170 175

Trp Leu Val Tyr Val Arg Ile Tyr Gln Ile Ala Lys Arg Arg Thr Arg
180 185 190

Val Pro Pro Ser Arg Arg Asp Pro Asp Ala Val Ala Ala Pro Pro Gly
195 200 205

Gly Thr Glu Arg Arg Pro Asn Gly Leu Gly Pro Glu Arg Ser Ala Gly
210 215 220

Pro Gly Gly Gly Arg Gly Arg Ser Ala Ser Gly Leu Pro Arg Arg Arg
225 230 235 240

Ala Gly Ala Gly Gly Gln Asn Arg Glu Lys Arg Phe Thr Phe Val Ile
245 250 255

Ala Val Val Ile Gly Val Phe Val Val Cys Trp Phe Pro Phe Phe Phe
260 265 270

Thr Tyr Thr Leu Thr Ala Val Leu Cys Ser Val Pro Arg Thr Leu Phe
275 280 285

Lys Phe Phe Phe Trp Phe Gly Tyr Cys Asn Ser Ser Leu Asn Pro Val
290 295 300

Ile Tyr Thr Ile Phe Asn His Asp Phe Arg Arg Ala Phe Lys Lys Ile
305 310 315 320

Leu Cys Arg Gly Asp Arg Lys Arg Ile Val
325 330

(2) INFORMATION FOR SEQ ID NO:22:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 334 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:22:
Thr Leu Thr Leu Val Cys Ile Ala Gly Leu Ile Met Leu Phe Thr Val
1 5 10 15

Phe Gly Asn Val Leu Val Ile Ile Ala Val Phe Thr Ser Arg Ala Leu
20 25 30

Lys Ala Pro Gln Asn Leu Phe Leu Val Ser Ile Ala Ser Ala Asp Ile
35 40 45

Leu Val Ala Thr Leu Val Ile Pro Phe Ser Leu Ala Asn Glu Val Met
50 55 60

Tyr Trp Tyr Phe Gly Lys Val Trp Cys Glu Ile Tyr Leu Ala Ile Asp
65 70 75 80

Val Leu Phe Cys Thr Ser Ser Ile Val His Leu Cys Ala Ile Ser Leu
85 90 95

Asp Arg Tyr Trp Ser Ile Thr Gln Ala Ile Glu Tyr Asn Leu Lys Arg
100 105 110

Thr Pro Arg Arg Ile Lys Ala Ile Ile Val Thr Val Trp Val Ile Ser
115 120 125

Ala Val Ile Ser Phe Pro Pro Leu Leu Ile Ser Ile Glu Lys Lys Gly
130 135 140

Ala Gly Gly Gly Gln Gln Pro Ala Glu Pro Ser Cys Lys Ile Asn Asp
145 150 155 160

Gln Lys Trp Tyr Val Ile Ser Ser Ser Ile Gly Ser Phe Phe Ala Pro

165 170 175

Cys Leu Ile Asn His Leu Val Tyr Val Arg Ile Tyr Gln Ile Ala Lys
180 185 190

Arg Arg Thr Arg Val Pro Pro Ser Arg Arg Gly Pro Asp Ala Cys Ser
195 200 205

Ala Pro Pro Gly Gly Ala Asp Arg Arg Pro Asn Ala Val Gly Pro Glu
210 215 220

Arg Gly Ala Gly Thr Ala Gly Gly Gln Gly Glu Glu Arg Ala Gly Gly
225 230 235 240

Ala Lys Ala Ser Arg Trp Arg Gly Arg Gln Asn Arg Glu Lys Arg Phe
245 250 255

Thr Phe Val Ile Ala Val Val Ile Gly Val Phe Val Val Cys Trp Phe
260 265 270

Pro Phe Phe Phe Thr Tyr Thr Leu Ile Ala Val Gly Cys Pro Val Pro
275 280 285

Tyr Gln Leu Phe Asn Phe Phe Phe Trp Phe Gly Tyr Cys Asn Ser Ser
290 295 300

Leu Asn Pro Val Ile Tyr Thr Ile Phe Asn His Asp Phe Arg Arg Ala
305 310 315 320

Phe Lys Lys Ile Leu Cys Arg Gly Asp Arg Lys Arg Ile Val
325 330

(2) INFORMATION FOR SEQ ID NO:23:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 321 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:23:

Leu Leu Thr Ala Leu Val Leu Ser Val Ile Ile Val Leu Thr Ile Ile
1 5 10 15

Gly Asn Ile Leu Val Ile Leu Ser Val Phe Thr Tyr Lys Pro Leu Arg
20 25 30

Ile Val Gln Asn Phe Phe Ile Val Ser Ile Ala Val Ala Asp Leu Thr
35 40 45

Val Ala Leu Leu Val Leu Pro Phe Trp Ala Tyr Ser Ile Leu Gly Arg
50 55 60

Trp Glu Phe Gly Ile His Leu Cys Lys Leu Trp Leu Thr Cys Asp Val
65 70 75 80

Leu Cys Cys Thr Ser Ser Ile Leu Asn Leu Cys Ala Ile Ala Leu Asp
85 90 95

Arg Tyr Trp Ala Ile Thr Asp Pro Ile Asn Tyr Ala Gln Lys Arg Thr
100 105 110

Val Gly Arg Val Leu Leu Leu Ile Ser Gly Val Trp Leu Leu Ser Leu
115 120 125

Leu Ile Ser Ser Pro Pro Leu Ile Gly Trp Asn Asp Trp Pro Asp Glu

130 135 140

Phe Thr Ser Ala Thr Pro Cys Glu Leu Thr Ser Gln Arg Ile Gly Tyr
145 150 155 160

Val Ile Tyr Ser Ser Leu Gly Ser Phe Phe Ile Pro Ile Ala Ile Met
165 170 175

Arg Ile Val Tyr Ile Glu Ile Phe Val Ala Thr Arg Arg Arg Leu Arg
180 185 190

Glu Arg Ala Arg Ala Asn Lys Ile Asn Thr Ile Ala Leu Lys Ser Thr
195 200 205

Glu Leu Glu Pro Met Ala Asn Ser Ser Pro Val Ala Ala Ser Asn Ser
210 215 220

Gly Ser Lys Lys Lys Thr Ser Gly Val Asn Gln Phe Ile Glu Glu Lys
225 230 235 240

Gln Lys Ile Ser Leu Ser Lys Glu Arg Arg Ala Ala Arg Thr Leu Gly
245 250 255

Ile Ile Met Val Phe Val Ile Cys Trp Leu Pro Phe Phe Ile Met Tyr
260 265 270

Val Ile Leu Pro Phe Cys Cys Pro Thr Asn Lys Phe Lys Asn Phe Ile
275 280 285

Thr Trp Leu Gly Tyr Ile Asn Ser Gly Leu Asn Pro Val Ile Tyr Thr
290 295 300

Ile Phe Asn Leu Asp Tyr Arg Arg Ala Phe Lys Arg Leu Leu Gly Leu
305 310 315 320

Asn

(2) INFORMATION FOR SEQ ID NO:24:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 373 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:24:

Arg Ile Leu Thr Ala Cys Phe Leu Ser Leu Leu Ile Leu Ser Thr Leu
1 5 10 15

Leu Gly Asn Thr Leu Val Cys Ala Ala Val Ile Arg Phe Arg His Leu
20 25 30

Arg Ser Lys Val Thr Asn Phe Phe Val Ile Ser Leu Ala Val Ser Asp
35 40 45

Leu Leu Val Ala Val Leu Leu Trp Lys Ala Val Ala Glu Ile Ala Gly
50 55 60

Phe Trp Pro Phe Gly Ser Phe Cys Asn Ile Trp Val Ala Phe Asp Ile
65 70 75 80

Met Cys Ser Thr Ala Ser Ile Leu Asn Leu Cys Val Ile Ser Val Asp
85 90 95

Arg Tyr Trp Ala Ile Ser Ser Pro Phe Arg Tyr Glu Arg Lys Lys Arg

100 105 110

Pro Lys Ala Ala Phe Ile Leu Ile Ser Val Ala Trp Thr Leu Ser Val
115 120 125

Leu Ile Ser Phe Ile Pro Val Gln Leu Ser Trp His Lys Ala Lys Pro
130 135 140

Thr Ser Pro Ser Asp Gly Met Ala Thr Ser Leu Ala Glu Thr Ile Asp
145 150 155 160

Asn Cys Asp Ser Ser Leu Ser Arg Thr Tyr Ala Ile Ser Ser Ser Val
165 170 175

Ile Ser Phe Tyr Ile Pro Val Ala Ile Leu Val Thr Tyr Thr Arg Ile
180 185 190

Tyr Arg Ile Ala Gln Lys Gln Ile Arg Arg Ile Ala Ala Leu Glu Arg
195 200 205

Ala Ala Val His Ala Lys Asn Cys Gln Gly Asn Lys Pro Val Glu Cys
210 215 220

Ser Gln Pro Glu Ser Ser Phe Met Ser Phe Lys Arg Glu Thr Lys Val
225 230 235 240

Leu Lys Thr Leu Ser Val Ile Thr Cys Val Phe Val Cys Cys Trp Leu
245 250 255

Pro Phe Phe Ile Leu Asn Cys Ile Leu Pro Phe Cys Gly Ser Gly Glu
260 265 270

Thr Gln Pro Phe Cys Thr Asp Ser Asn Thr Phe Asp Val Phe Val Trp
275 280 285

Phe Gly Trp Ala Asn Ser Ser Leu Asn Pro Ile Ile Tyr Ala Phe Asn
290 295 300

Ala Asp Phe Arg Lys Ala Phe Ser Thr Leu Leu Gly Cys Tyr Arg Leu
305 310 315 320

Cys Pro Ala Thr Asn Met Ala Ile Glu Thr Val Ser Ile Asn Asn Gly
325 330 335

Ala Ala Met Phe Ser Ser His His Glu Pro Arg Gly Ser Ile Ser Lys
340 345 350

Glu Cys Asn Leu Val Tyr Leu Ile Pro His Ala Val Gly Ser Ser Glu
355 360 365

Asp Leu Lys Lys Glu
370

(2) INFORMATION FOR SEQ ID NO:25:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 360 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:25:
Gln Trp Thr Ala Cys Leu Leu Thr Leu Leu Ile Ile Trp Thr Leu Leu
1 5 10 15

Gly Asn Val Leu Val Cys Ala Ala Ile Val Arg Ser Arg His Leu Leu
20 25 30

Val Phe Ile Val Ser Ile Ala Val Ser Asp Leu Phe Val Ala Leu Leu
35 40 45

Val Asn Thr Trp Lys Ala Tyr Ala Glu Val Ala Gly Tyr Trp Pro Phe
50 55 60

Gly Ala Phe Cys Asp Val Trp Val Ala Phe Asp Ile Met Cys Ser Thr
65 70 75 80

Ala Ser Ile Leu Asn Leu Cys Val Ile Ser Val Asp Arg Tyr Trp Ala
85 90 95

Ile Ser Arg Pro Phe Arg Tyr Lys Ala Leu Val Met Val Gly Ile Ala
100 105 110

Trp Thr Leu Ser Ile Leu Ile Ser Phe Ile Pro Val Gln Ile Asn Trp
115 120 125

Asn Arg Asp Gln Ala Ala Ser Trp Gly Gly Leu Asp Leu Pro Asn Asn
130 135 140

Ile Asp Cys Asp Ser Ser Leu Asn Arg Thr Tyr Ala Ile Ser Ser Ser
145 150 155 160

Leu Ile Ser Phe Tyr Ile Pro Val Ala Ile Leu Val Thr Tyr Thr Arg
165 170 175

Ile Tyr Arg Ile Ala Gln Val Gln Ile Arg Arg Ile Ser Ser Leu Glu
180 185 190

Arg Ala Ala Glu His Ala Gln Ser Cys Arg Ser Ser Ala Ala Cys Ala
195 200 205

Pro Asp Thr Ser Leu Arg Ala Ser Ile Lys Lys Glu Thr Lys Val Leu
210 215 220

Lys Thr Leu Ser Val Ile Ile Cys Val Phe Val Cys Cys Trp Leu Pro
225 230 235 240

Phe Phe Ile Leu Asn Cys Met Val Pro Phe Cys Ser Gly His Pro Glu
245 250 255

Gly Pro Pro Ala Gly Phe Pro Cys Val Ser Glu Thr Thr Phe Asp Val
260 265 270

Phe Val Trp Phe Gly Trp Ala Asn Ser Ser Leu Asn Pro Val Ile Tyr
275 280 285

Ala Phe Asn Ala Asp Phe Gln Lys Val Phe Ala Gln Leu Leu Cys Ser
290 295 300

His Phe Cys Ser Arg Thr Pro Val Glu Thr Val Asn Ile Ser Asn Glu
305 310 315 320

Leu Ile Ser Tyr Asn Gln Asp Ile Val Phe His Lys Glu Ile Ala Ala
325 330 335

Ala Tyr Ile His Met Met Pro Asn Ala Val Thr Pro Gly Asn Arg Glu
340 345 350

Val Asp Asn Asp Glu Glu Glu Gly
355 360

(2) INFORMATION FOR SEQ ID NO:26:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 314 amino acids
(B) TYPE: amino acid

(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:26:

Tyr Asn Tyr Tyr Ala Thr Leu Leu Thr Leu Leu Ile Ala Val Ile Val
1 5 10 15

Phe Gly Asn Val Leu Val Cys Met Ala Val Ser Arg Glu Lys Ala Leu
20 25 30

Gln Thr Met Asn Tyr Leu Ile Val Ser Ile Ala Val Ala Asp Leu Leu
35 40 45

Val Ala Thr Leu Val Trp Trp Trp Tyr Leu Glu Val Val Gly Glu Trp
50 55 60

Lys Phe Ser Arg Ile His Cys Asp Ile Phe Val Thr Leu Asp Ile Thr
65 70 75 80

Ala Ser Ile Leu Asn Leu Cys Ala Ile Ser Ile Asp Arg Tyr Thr Ala
85 90 95

Val Ala Met Pro Met Leu Tyr Asn Thr Arg Tyr Ser Ser Lys Arg Arg
100 105 110

Val Thr Val Met Ile Ser Ile Val Trp Val Leu Ser Phe Thr Ile Ser
115 120 125

Cys Pro Leu Leu Phe Gly Leu Asn Asn Ala Asp Gln Asn Glu Cys Ile
130 135 140

Ile Ala Asn Pro Ala Phe Val Val Tyr Ser Ser Ile Val Se. Phe Tyr
145 150 155 160

Val Pro Phe Ile Val Thr Leu Leu Val Tyr Ile Lys Ile Tyr Ile Val
165 170 175

Leu Arg Arg Arg Arg Lys Arg Val Asn Thr Lys Arg Ser Ser Arg Ala
180 185 190

Phe Arg Ala His Leu Arg Ala Pro Leu Lys Gly Asn Cys Thr His Pro
195 200 205

Glu Asp Met Lys Leu Cys Thr Val Ile Pro Asn Gly Lys Thr Arg Thr
210 215 220

Ser Leu Lys Thr Met Ser Arg Arg Lys Leu Ser Gln Gln Lys Glu Lys
225 230 235 240

Lys Ala Thr Gln Met Ile Ala Ile Val Leu Gly Val Phe Ile Ile Cys
245 250 255

Lys Leu Pro Phe Phe Ile Thr His Ile Leu Asn Ile His Cys Asp Cys
260 265 270

Asn Ile Pro Pro Val Leu Tyr Ser Ala Phe Thr Trp Leu Gly Tyr Val
275 280 285

Asn Ser Ala Val Asn Pro Ile Ile Tyr Thr Thr Phe Asn Ile Glu Phe
290 295 300

Arg Lys Ala Phe Leu Lys Ile Leu His Cys
305 310

(2) INFORMATION FOR SEQ ID NO:27:
(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 317 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:27:

Ala Tyr Tyr Ala Leu Ser Tyr Cys Ala Leu Ile Leu Ala Ile Val Phe
1 5 10 15

Gly Asn Gly Leu Val Cys Met Ala Val Leu Arg Glu Lys Ala Leu Gln
20 25 30

Thr Thr Thr Asn Tyr Leu Val Val Ser Leu Ala Val Ala Asp Leu Leu
35 40 45

Val Ala Thr Leu Val Trp Trp Val Val Tyr Leu Glu Val Thr Gly Gly
50 55 60

Val Trp Asn Phe Ser Arg Ile Cys Cys Asp Val Phe Val Thr Leu Asp
65 70 75 80

Val Met Met Thr Ala Ser Ile Leu Asn Leu Cys Ala Ile Ser Ile Asp
85 90 95

Arg Tyr Thr Ala Val His Tyr Gln His Gly Thr Gly Gln Ser Ser Cys
100 105 110

Arg Arg Val Ala Ile Met Ile Thr Ala Val Trp Val Leu Ala Phe Ala
115 120 125

Val Ser Cys Pro Leu Leu Phe Gly Phe Asn Thr Gly Asp Pro Thr Val
130 135 140

Cys Ser Ile Ser Asn Pro Asp Phe Val Ile Tyr Ser Ser Val Val Ser
145 150 155 160

Phe Tyr Leu Pro Phe Gly Val Thr Val Leu Val Tyr Ala Arg Ile Tyr
165 170 175

Val Val Leu Lys Gln Arg Arg Arg Lys Arg Ile Leu Thr Arg Gln Asn
180 185 190

Ser Gln Cys Asn Ser Val Arg Pro Gly Phe Pro Gln Gln Ser Thr Ser
195 200 205

Leu Pro Asp Pro Ala His Leu Glu Leu Lys Arg Ser Asn Gly Arg Leu
210 215 220

Ser Thr Ser Leu Lys Leu Pro Leu Gln Pro Arg Gly Val Pro Leu Arg
225 230 235 240

Glu Lys Lys Ala Thr Gln Met Val Ala Ile Val Leu Gly Ala Phe Ile
245 250 255

Val Cys Trp Leu Pro Phe Phe Leu Thr His Val Ile Asn Thr His Cys
260 265 270

Gln Thr Cys His Val Ser Pro Glu Leu Tyr Ser Ala Thr Thr Trp Leu
275 280 285

Gly Tyr Val Asn Ser Ala Leu Asn Pro Val Ile Tyr Thr Thr Phe Asn
290 295 300

Ile Glu Phe Arg Lys Ala Phe Leu Lys Ile Leu Ser Cys
305 310 315

(2) INFORMATION FOR SEQ ID NO:28:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 315 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:28:

```
Gly Ala Ala Ala Leu Val Gly Gly Val Leu Leu Ile Cys Ala Val Leu
1               5                  10                  15

Ala Gly Asn Ser Leu Val Cys Val Ser Val Ala Thr Glu Arg Ala Leu
            20                  25                  30

Gln Thr Pro Thr Asn Ser Phe Ile Val Ser Leu Ala Ala Ala Asp Leu
        35                  40                  45

Leu Leu Ala Leu Leu Val Leu Pro Leu Phe Val Tyr Ser Glu Val Gln
    50                  55                  60

Gly Ala Ala Trp Leu Leu Ser Pro Arg Leu Cys Asp Val Met Leu Cys
65                  70                  75                  80

Thr Ala Ser Ile Phe Asn Leu Cys Ala Ile Ser Val Asp Arg Phe Val
                85                  90                  95

Ala Val Ala Val Pro Leu Arg Tyr Asn Arg Gln Gly Gly Ser Arg Arg
            100                 105                 110

Gln Leu Leu Leu Ile Gly Ala Thr Trp Leu Leu Ser Ala Ala Val Ala
        115                 120                 125

Ala Pro Val Leu Cys Gly Leu Asn Asp Val Arg Gly Arg Asp Pro Ala
    130                 135                 140

Val Cys Arg Leu Glu Asp Arg Asp Tyr Val Val Tyr Ser Ser Val Cys
145                 150                 155                 160

Ser Phe Phe Leu Pro Cys Pro Leu Leu Tyr Trp Ala Thr Phe Arg Gly
                165                 170                 175

Leu Gln Leu Val Ala Arg Arg Ala Lys Leu His Gly Arg Ala Pro Arg
            180                 185                 190

Arg Pro Ser Gly Pro Gly Pro Pro Ser Pro Thr Pro Pro Ala Pro Arg
        195                 200                 205

Leu Pro Gln Asp Pro Cys Gly Ala Leu Pro Pro Gln Thr Pro Pro Gln
    210                 215                 220

Thr Arg Arg Arg Arg Ala Lys Ile Thr Gly Arg Glu Arg Lys Ala
225                 230                 235                 240

Met Arg Val Leu Pro Val Val Val Gly Ala Phe Ile Leu Cys Trp Thr
                245                 250                 255

Pro Phe Phe Val Val His Ile Thr Gln Ala Leu Cys Pro Ala Cys Ser
            260                 265                 270

Val Pro Pro Arg Leu Val Ser Ala Val Thr Trp Leu Ser Tyr Val Asn
        275                 280                 285

Ser Ala Ile Asn Pro Val Ile Tyr Thr Val Phe Asn Ala Glu Phe Arg
    290                 295                 300

Asn Val Phe Arg Lys Ala Leu Arg Ala Cys Cys
```

305 310 315

(2) INFORMATION FOR SEQ ID NO:29:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 327 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:29:

Lys Ile Ser Leu Ala Val Val Leu Ser Val Ile Thr Leu Ala Thr Val
1 5 10 15

Leu Ser Asn Ala Phe Val Leu Thr Arg Ile Leu Leu Thr Arg Lys Leu
20 25 30

His Thr Pro Ala Asn Tyr Leu Ile Gly Ser Ile Ala Thr Thr Asp Leu
35 40 45

Leu Val Ser Ile Leu Val Trp Ile Ser Ile Ala Tyr Thr Ile Thr His
50 55 60

Thr Trp Asn Phe Gly Gln Ile Leu Cys Asp Ile Trp Leu Ser Ser Asp
65 70 75 80

Ile Thr Cys Cys Thr Ala Ser Ile Leu His Leu Cys Val Ile Ala Leu
85 90 95

Asp Arg Tyr Trp Ala Ile Thr Asp Ala Leu Glu Tyr Ser Lys Arg Arg
100 105 110

Thr Ala Gly His Ala Ala Thr Met Ile Ala Ile Val Trp Ala Ile Ser
115 120 125

Ile Cys Ile Ser Ile Pro Pro Leu Phe Trp Arg Ala Lys Ala Gln Glu
130 135 140

Glu Met Ser Asp Cys Leu Val Asn Thr Ser Gln Ser Tyr Thr Ile Tyr
145 150 155 160

Ser Thr Cys Gly Ala Phe Tyr Ile Pro Ser Val Leu Leu Ile Ile Leu
165 170 175

Tyr Gly Arg Ile Tyr Arg Ala Ala Arg Asn Arg Ile Leu Asn Pro Pro
180 185 190

Ser Leu Tyr Gly Lys Arg Phe Thr Thr Ala His Leu Ile Thr Gly Ser
195 200 205

Ala Gly Ser Ser Leu Cys Ser Leu Asn Ser Ser Leu His Glu Gly His
210 215 220

Asn His Val Lys Ile Lys Leu Ala Asp Ser Ala Leu Glu Arg Lys Arg
225 230 235 240

Ile Ser Ala Ala Arg Glu Arg Lys Ala Thr Lys Ile Leu Gly Ile Ile
245 250 255

Leu Gly Ala Phe Ile Ile Cys Trp Leu Pro Phe Phe Val Val Ser Leu
260 265 27

Val Leu Pro Ile Cys Arg Asp Ser Cys Trp Ile His Pro Ala Leu Phe
275 280 285

Asp Phe Phe Thr Trp Leu Gly Tyr Ile Asn Ser Leu Ile Asn Pro Ile
290 295 300

Ile Tyr Thr Val Phe Asn Glu Glu Phe Arg Gln Ala Phe Gln Lys Ile
305 310 315 320

Val Pro Phe Arg Lys Ala Ser
325

(2) INFORMATION FOR SEQ ID NO:30:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 325 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:30:
Val Ile Thr Ser Leu Leu Leu Gly Thr Leu Ile Phe Cys Ala Val Leu
1 5 10 15

Gly Asn Ala Cys Val Val Ala Ala Ile Ala Leu Glu Arg Ser Leu Gln
20 25 30

Asn Val Ala Asn Tyr Leu Ile Gly Ser Leu Ala Val Arg Asp Leu Met
35 40 45

Val Ser Val Leu Val Leu Pro Met Ala Ala Leu Tyr Gln Val Leu Asn
50 55 60

Lys Trp Thr Leu Gly Gln Val Thr Cys Asp Leu Phe Ile Ala Leu Asp
65 70 75 80

Val Leu Cys Cys Thr Ser Ser Ile Leu His Leu Cys Ala Ile Ala Leu
85 90 95

Asp Arg Tyr Trp Ala Ile Thr Asp Pro Ile Asp Tyr Val Asn Lys Arg
100 105 110

Thr Pro Arg Pro Arg Ala Leu Ile Ser Leu Thr Trp Leu Ile Gly Phe
115 120 125

Leu Ile Ser Ile Pro Pro Met Leu Gly Trp Arg Thr Pro Glu Asp Arg
130 135 140

Ser Asp Pro Asp Ala Cys Thr Ile Ser Lys Asp His Gly Tyr Thr Ile
145 150 155 160

Tyr Ser Thr Ile Phe Ala Phe Tyr Ile Pro Leu Leu Leu Met Leu Val
165 170 175

Leu Tyr Gly Arg Ile Phe Arg Ala Ala Arg Phe Arg Ile Arg Lys Thr
180 185 190

Val Lys Lys Val Glu Lys Thr Gly Ala Asp Thr Arg His Gly Ala Ser
195 200 205

Pro Ala Pro Gln Pro Lys Lys Ser Val Asn Gly Glu Ser Gly Ser Arg
210 215 220

Asn Ala Ser Phe Glu Arg Lys Asn Glu Arg Asn Ala Phe Ala Lys Leu
225 230 235 240

Leu Ala Arg Glu Arg Lys Thr Val Lys Thr Leu Gly Ile Ile Met Thr
245 250 255

Phe Ile Leu Cys Trp Leu Pro Phe Phe Ile Val Ala Leu Val Leu Pro
260 265 270

Phe Cys Glu Ser Ser Cys His Met Pro Thr Leu Ile Arg Ala Ile Ile

275 280 285

Asn Trp Leu Cys Val Ile Asn Ser Leu Leu Asn Pro Val Ile Tyr Ala
290 295 300

Tyr Phe Asn Lys Asp Phe Gln Asn Ala Phe Lys Lys Ile Ile Lys Cys
305 310 315 320

Asn Phe Cys Arg Gln
325

(2) INFORMATION FOR SEQ ID NO:31:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 385 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:31:
Gln Asn Trp Pro Ala Leu Ser Ile Val Val Ile Ile Ile Asn Thr Ile
1 5 10 15

Gly Gly Asn Ile Leu Val Ile Met Ala Val Ser Lys Lys Leu His Asn
20 25 30

Ala Thr Asn Tyr Phe Leu Met Ser Ile Ala Ile Ala Asp Me· Leu Val
35 40 45

Gly Phe Leu Val Trp Leu Ser Leu Leu Ala Ile Leu Tyr Asp Tyr Val
50 55 60

Trp Pro Leu Pro Arg Tyr Leu Cys Pro Val Trp Ile Ser Leu Asp Val
65 70 75 80

Leu Phe Ser Thr Ala Ser Ile Met His Leu Cys Ala Ile Ser Leu Asp
85 90 95

Arg Tyr Val Ala Ile Arg Asn Pro Ile Glu His Ser Arg Phe Ser Arg
100 105 110

Thr Lys Ala Ile Met Lys Ile Ala Ile Val Trp Ala Ile Ser Ile Gly
115 120 125

Val Ser Val Pro Ile Pro Val Ile Gly Leu Arg Asp Glu Ser Lys Val
130 135 140

Phe Val Asn Asn Thr Thr Ile Cys Val Leu Asn Asp Pro Asn Phe Val
145 150 155 160

Leu Ile Gly Ser Phe Val Ala Phe Phe Ile Pro Thr Leu Ile Met Val
165 170 175

Ile Thr Tyr Phe Leu Thr Ile Tyr Val Leu Arg Arg Gln Th. Leu Met
180 185 190

Leu Leu Arg Gly His Thr Glu Glu Glu Ile Ala Met Ser Leu Asn Phe
195 200 205

Leu Asn Cys Cys Cys Lys Lys Asn Gly Gly Glu Glu Glu Asn Ala Pro
210 215 220

Asn Asn Pro Asn Pro Asp Gln Lys Pro Arg Arg Lys Lys Lys Glu Lys
225 230 235 240

Arg Pro Arg Gly Thr Met Gln Ala Ile Asn Asn Glu Lys Lys Ala Ser
245 250 255

Lys Val Leu Gly Ile Val Phe Phe Val Phe Leu Ile Met Trp Cys Pro
260 265 270

Phe Phe Ile Thr Asn Ile Leu Ser Val Leu Cys Gly Lys Ala Cys Asn
275 280 285

Gln Cys Lys Leu Leu Asn Val Phe Val Trp Ile Gly Tyr Val Cys Ser
290 295 300

Gly Ile Asn Pro Val Ile Tyr Thr Leu Phe Asn Lys Ile Tyr Arg Arg
305 310 315 320

Ala Phe Ser Lys Tyr Leu Arg Cys Asp Tyr Lys Pro Asp Lys Lys Pro
325 330 335

Pro Val Arg Gln Ile Pro Arg Val Ala Ala Thr Ala Leu Ser Gly Arg
340 345 350

Glu Leu Asn Val Asn Ile Tyr Arg His Thr Asn Glu Arg Val Ala Arg
355 360 365

Lys Ala Asn Asp Pro Glu Pro Gly Ile Glu Asn Gln Val Glu Asn Leu
370 375 380

Glu
385

(2) INFORMATION FOR SEQ ID NO:32:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 379 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:32:
Lys Asn Trp Ser Ala Leu Leu Thr Thr Val Val Ile Ile Leu Thr Ile
1 5 10 15

Ala Gly Asn Ile Leu Val Ile Met Ala Val Ser Leu Glu Lys Lys Leu
20 25 30

Gln Asn Ala Thr Asn Tyr Phe Leu Met Ser Leu Ala Ile Ala Asp Met
35 40 45

Leu Leu Gly Phe Leu Val Trp Val Ser Asn Glu Thr Ile Leu Tyr Gly
50 55 60

Tyr Arg Trp Pro Leu Pro Ser Lys Leu Cys Ala Ile Trp Ile Tyr Leu
65 70 75 80

Asp Val Leu Phe Ser Thr Ala Ser Ile Met His Leu Cys Ala Ile Ser
85 90 95

Leu Asp Arg Tyr Val Ala Ile Gln Asn Pro Ile His His Ser Arg Phe
100 105 110

Asn Ser Arg Thr Lys Ala Phe Leu Lys Ile Ile Ala Val Trp Thr Ile
115 120 125

Ser Val Gly Ile Ser Met Pro Ile Pro Val Phe Gly Leu Gln Asp Asp
130 135 140

Ser Lys Val Phe Lys Glu Gly Ser Cys Leu Leu Ala Asp Asp Asn Phe
145 150 155 160

Val Leu Ile Gly Ser Phe Val Ala Phe Phe Ile Pro Leu Thr Ile Met
165 170 175

Val Ile Thr Tyr Phe Leu Thr Ile Lys Ser Leu Arg Gln Lys Phe Ala
180 185 190

Thr Leu Cys Val Ser Asp Leu Ser Thr Arg Ala Lys Leu Ala Ser Phe
195 200 205

Ser Phe Leu Pro Gln Ser Ser Leu Ser Ser Glu Lys Leu Phe Gln Arg
210 215 220

Ser Ile His Arg Glu Pro Gly Ser Tyr Ala Gly Arg Lys Thr Met Gln
225 230 235 240

Ser Ile Ser Asn Glu Gln Lys Ala Cys Lys Val Leu Gly Ile Val Phe
245 250 255

Phe Leu Phe Val Val Met Trp Cys Pro Phe Phe Ile Thr Asn Ile Met
260 265 270

Val Ile Cys Lys Glu Ser Cys Asn Glu Asn Val Ile Gly Ala Leu Leu
275 280 285

Asn Val Phe Val Trp Ile Gly Tyr Leu Ser Ser Ala Val Asn Pro Leu
290 295 300

Val Tyr Thr Leu Phe Asn Lys Thr Tyr Arg Ser Ala Phe Ser Arg Tyr
305 310 315 320

Leu Gln Cys Gln Tyr Lys Glu Asn Arg Lys Pro Leu Leu Ile Leu Val
325 330 335

Asn Thr Ile Pro Ala Leu Ala Tyr Lys Ser Ser Gln Leu Gln Val Gly
340 345 350

Gln Lys Lys Asn Ser Gln Glu Asp Ala Glu Gln Thr Val Asp Asp Cys
355 360 365

Ser Met Val Thr Leu Gly Lys Gln Gln Ser Glu
370 375

(2) INFORMATION FOR SEQ ID NO:33:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 337 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:33:
Ile Thr Ile Thr Val Val Leu Ala Val Leu Ile Leu Ile Thr Val Ala
1 5 10 15

Gly Asn Val Val Val Cys Ile Ala Val Gly Ile Asn Arg Arg Leu Arg
20 25 30

Asn Leu Thr Asn Cys Phe Ile Val Ser Leu Ala Ile Thr Asp Leu Leu
35 40 45

Leu Gly Leu Leu Val Leu Pro Phe Ser Ala Ile Tyr Gln Leu Ser Cys
50 55 60

Lys Trp Ser Phe Gly Lys Val Phe Cys Asn Ile Tyr Thr Ser Leu Asp
65 70 75 80

Val Met Leu Cys Thr Ala Ser Ile Leu Asn Leu Leu Ile Ser Leu Asp

85 90 95

Arg Tyr Cys Ala Val Met Asp Pro Leu Arg Tyr Pro Val Leu Val Arg
100 105 110

Pro Val Arg Val Ala Ile Ser Leu Val Leu Ile Trp Val Ile Ser Ile
115 120 125

Thr Leu Ser Phe Leu Ser Ile His Leu Gly Trp Asn Ser Arg Asn Glu
130 135 140

Thr Ser Lys Gly Asn His Thr Thr Ser Lys Cys Lys Val Gln Val Asn
145 150 155 160

Glu Val Tyr Gly Leu Val Asp Gly Leu Val Thr Phe Tyr Leu Pro Leu
165 170 175

Leu Ile Met Cys Ile Thr Tyr Tyr Arg Ile Phe Lys Val Ala Arg Asp
180 185 190

Ala Lys Arg Asn His Ile Ser Ser Trp Lys Ala Ala Thr Ile Arg Glu
195 200 205

His Lys Ala Thr Val Thr Ile Ala Ala Val Met Ala Phe Ile Ile Cys
210 215 220

Trp Phe Pro Tyr Phe Thr Ala Phe Val Tyr Arg Gly Leu Arg Gly Asp
225 230 235 240

Asp Ala Ile Asn Glu Val Leu Glu Ala Ile Val Leu Trp Leu Gly Tyr
245 250 255

Ala Asn Ser Ala Leu Asn Pro Ile Leu Tyr Ala Ala Leu Asn Arg Asp
260 265 270

Phe Arg Thr Gly Tyr Gln Gln Leu Phe Cys Cys Arg Ile Ala Asn Arg
275 280 285

Asn Ser His Lys Thr Ser Leu Arg Ser Asn Ala Ser Gln Leu Ser Arg
290 295 300

Thr Gln Ser Arg Glu Pro Arg Gln Gln Glu Glu Lys Pro Leu Lys Leu
305 310 315 320

Gln Val Trp Ser Gly Thr Glu Val Thr Ala Pro Gln Gly Ala Thr Asp
325 330 335

Arg

(2) INFORMATION FOR SEQ ID NO:34:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 315 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:34:
Ile Ile Thr Tyr Leu Val Phe Ala Val Arg Phe Val Leu Gly Val Leu
1 5 10 15

Gly Asn Gly Leu Val Ile Trp Val Ala Gly Phe Arg Met Thr His Thr
20 25 30

Val Thr Thr Ile Ser Tyr Leu Asn Leu Ala Val Ala Asp Phe Cys Phe

35 40 45

Thr Ser Thr Leu Pro Phe Phe Met Val Arg Leu Gly His Trp Pro Phe
50 55 60

Gly Trp Phe Leu Cys Lys Phe Leu Phe Thr Ile Val Asp Ile Asn Leu
65 70 75 80

Phe Gly Ser Val Phe Leu Ile Ala Leu Ile Ala Leu Asp Arg Cys Val
85 90 95

Cys Val Leu His Pro Val Trp Thr Gln Asn His Arg Thr Val Ser Leu
100 105 110

Ala Lys Lys Val Ile Ile Gly Pro Trp Val Met Ala Leu Leu Leu Thr
115 120 125

Leu Pro Val Ile Ile Arg Val Thr Ile Val Pro Gly Lys Thr Gly Thr
130 135 140

Val Ala Cys Thr Phe Asn Phe Ser Pro Trp Thr Asn Asp Pro Lys Glu
145 150 155 160

Arg Ile Asn Val Ala Val Ala Met Leu Thr Val Arg Gly Ile Ile Arg
165 170 175

Phe Ile Ile Gly Phe Ser Ala Pro Met Ser Ile Val Ala Val Ser Tyr
180 185 190

Gly Leu Ile Ala Thr Lys Ile Ile Lys Ser Ser Arg Pro Leu Arg Val
195 200 205

Leu Ser Phe Val Ala Ala Ala Phe Phe Leu Cys Trp Ser Pro Tyr Gln
210 215 220

Val Val Ala Leu Ile Ala Thr Val Arg Ile Arg Glu Leu Leu Gln Gly
225 230 235 240

Met Tyr Lys Glu Ile Gly Ile Ala Val Asp Val Thr Ser Ala Ile Ala
245 250 255

Phe Phe Asn Ser Cys Leu Asn Pro Leu Tyr Val Phe Met Gly Gln Asp
260 265 270

Phe Arg Glu Arg Leu Ile His Ala Leu Pro Ala Ser Leu Glu Arg Ala
275 280 285

Leu Thr Glu Asp Ser Thr Gln Thr Ser Asp Thr Ala Thr Asn Ser Thr
290 295 300

Leu Pro Ser Ala Glu Val Ala Leu Gln Ala Lys
305 310 315

(2) INFORMATION FOR SEQ ID NO:35:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 304 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:35:
Asp Ile Leu Ala Leu Val Ile Phe Ala Val Val Phe Leu Val Gly Val
1 5 10 15

Leu Gly Asn Ala Leu Val Val Trp Val Thr Ala Phe Glu Ala Lys Arg

Thr Ile Asn Ala Ile Trp Phe Leu Asn Ile Ala Val Ala Asp Phe Leu
20 25 30
35 40 45

Ser Cys Leu Ala Leu Pro Ile Leu Phe Thr Ser Ile Val Gln His His
50 55 60

His Trp Pro Phe Gly Gly Ala Ala Cys Ser Ile Leu Pro Ser Leu Ile
65 70 75 80

Leu Leu Asn Met Tyr Ala Ser Ile Leu Leu Leu Ala Thr Ile Ser Ala
85 90 95

Asp Arg Phe Leu Leu Val Phe Lys Pro Ile Trp Cys Gln Asn Phe Arg
100 105 110

Gly Ala Gly Leu Ala Trp Ile Ala Cys Ala Val Ala Trp Gly Ile Ala
115 120 125

Leu Leu Leu Thr Ile Pro Ser Phe Leu Tyr Arg Val Val Arg Glu Glu
130 135 140

Tyr Phe Pro Pro Lys Val Leu Cys Gly Cys Asp Tyr Ser His Asp Lys
145 150 155 160

Arg Arg Glu Arg Ala Val Ala Ile Val Arg Leu Val Leu Gly Phe Leu
165 170 175

Trp Pro Leu Leu Thr Leu Thr Ile Cys Tyr Thr Thr Arg Ser Thr Lys
180 185 190

Thr Leu Lys Val Val Val Ala Val Val Ala Ser Phe Phe Ile Phe Trp
195 200 205

Leu Pro Tyr Gln Val Thr Gly Ile Met Met Ser Phe Leu Glu Pro Ser
210 215 220

Ser Pro Thr Phe Leu Leu Leu Asn Lys Leu Asp Ser Leu Cys Val Ser
225 230 235 240

Phe Ala Tyr Ile Asn Cys Cys Ile Asn Pro Ile Ile Tyr Val Val Ala
245 250 255

Gly Gln Gly Gln Phe Gln Gly Arg Leu Arg Lys Ser Leu Pro Ser Leu
260 265 270

Leu Arg Asn Val Leu Thr Glu Glu Ser Val Val Arg Glu Ser Lys Ser
275 280 285

Phe Thr Arg Ser Thr Val Asp Thr Met Ala Gln Lys Thr Gln Ala Val
290 295 300

(2) INFORMATION FOR SEQ ID NO:36:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 322 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:36:
Thr Leu Phe Val Pro Ser Val Tyr Thr Gly Val Phe Val Val Ser Leu
1 5 10 15

Pro Leu Asn Ile Met Ala Ile Val Val Phe Ile Leu Lys Met Lys Val

Lys Lys Pro Ala Val His Ile Ala Thr Ala Asp Val Leu Phe Val Ser
35 40 45

Val Leu Pro Phe Lys Ile Ser Tyr Tyr Phe Ser Gly Ser Asp Trp Gln
50 55 60

Phe Gly Ser Glu Leu Cys Arg Phe Val Thr Ala Ala Phe Tyr Cys Asn
65 70 75 80

Met Tyr Ala Ser Ile Leu Leu Ile Ser Ile Asp Arg Phe Ile Ala Val
85 90 95

Val Tyr Pro Met Gln Ser Leu Ser Trp Arg Thr Leu Gly Arg Ala Ser
100 105 110

Phe Thr Cys Ile Ala Ile Trp Ala Ile Ala Ile Ala Gly Val Pro Leu
115 120 125

Val Leu Lys Glu Gln Thr Ile Gln Val Pro Gly Leu Asn Ile Thr Thr
130 135 140

Ile Cys His Asp Val Leu Asn Glu Thr Leu Leu Glu Gly Tyr Tyr Ala
145 150 155 160

Tyr Tyr Phe Ser Ala Phe Ser Ala Val Phe Phe Phe Val Pro Leu Ile
165 170 175

Ile Ser Thr Val Cys Tyr Val Ser Ile Ile Arg Cys Leu Ser Ser Ser
180 185 190

Ala Val Ala Asn Arg Ser Lys Lys Ser Arg Thr Asn Arg Cys Phe Asn
195 200 205

Ser Thr Val Ala Leu Phe Leu Ser Ala Ala Val Phe Cys Ile Phe Ile
210 215 220

Ile Cys Phe Gly Pro Thr Trp Leu Leu Ile Ala His Tyr Ser Phe Leu
225 230 235 240

Ser His Thr Ser Thr Thr Glu Ala Ala Tyr Phe Ala Tyr Leu Leu Cys
245 250 255

Val Cys Val Ser Ser Ile Ser Ser Cys Ile Asp Pro Leu Ile Tyr Tyr
260 265 270

Tyr Ala Ser Ser Glu Cys Gln Arg Tyr Val Tyr Ser Ile Leu Cys Cys
275 280 285

Lys Glu Ser Ser Asp Pro Ser Ser Tyr Asn Ser Ser Gly Gln Leu Met
290 295 300

Ser Leu Thr Cys Ser Ser Asn Leu Asn Asn Ser Ile Tyr Lys Lys Leu
305 310 315 320

Leu Thr

(2) INFORMATION FOR SEQ ID NO:37:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 311 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:37:

Tyr Ile Asn Thr Val Ile Ser Cys Thr Ile Phe Ile Val Gly Trp Gly
1 5 10 15

Asn Ala Thr Leu Leu Arg Ile Ile Tyr Gln Asn Lys Cys Met Arg Asn
20 25 30

Gly Pro Asn Ala Leu Ile Ala Ser Ile Ala Leu Gly Asp Leu Ile Tyr
35 40 45

Val Val Ile Asp Leu Pro Ile Asn Val Pro Lys Leu Ile Ala Gly Arg
50 55 60

Trp Pro Phe Glu Gln Asn Asp Phe Gly Val Phe Cys Lys Phe Met Gly
65 70 75 80

Val Val Met Ile Phe Phe Gly Leu Ser Pro Leu Leu Leu Gly Ala Ala
85 90 95

Met Ala Ser Glu Arg Tyr Leu Gly Ile Thr Arg Pro Phe Ser Arg Pro
100 105 110

Ala Val Ala Ser Gln Arg Arg Ala Trp Ala Thr Val Gly Leu Val Trp
115 120 125

Ala Ala Ala Leu Ala Leu Gly Leu Leu Pro Leu Leu Gly Val Gly Arg
130 135 140

Tyr Thr Val Gln Tyr Pro Gly Ser Trp Cys Phe Leu Thr Leu Gly Ala
145 150 155 160

Glu Ser Gly Asp Val Ala Phe Gly Leu Leu Phe Ser Gly Leu Ser Val
165 170 175

Gly Leu Ser Phe Leu Leu Asn Thr Val Ser Val Ala Thr Leu His His
180 185 190

Val Tyr His Gly Gln Glu Ala Ala Gln Gln Arg Pro Arg Asp Ser Glu
195 200 205

Val Glu Met Met Ala Gln Leu Leu Gly Ile Met Val Val Ala Ser Val
210 215 220

Cys Trp Leu Pro Leu Leu Val Phe Ile Ala Gln Thr Val Leu Arg Asn
225 230 235 240

Pro Pro Ala Met Ser Pro Ala Gly Gln Leu Ser Arg Thr Thr Glu Lys
245 250 255

Glu Leu Leu Ile Tyr Leu Arg Val Ala Thr Trp Asn Gln Ile Leu Asp
260 265 270

Pro Trp Val Tyr Ile Leu Phe Arg Arg Ala Val Leu Arg Arg Leu Gln
275 280 285

Pro Arg Leu Ser Thr Arg Pro Arg Ser Leu Ser Leu Gln Pro Gln Leu
290 295 300

Thr Gln Arg Ser Gly Leu Gln
305 310

(2) INFORMATION FOR SEQ ID NO:38:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 312 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:38:

Lys Tyr Phe Val Val Ile Ile Tyr Ala Leu Val Phe Leu Leu Ser Leu
1 5 10 15

Leu Gly Asn Ser Leu Val Met Leu Val Ile Leu Tyr Ser Arg Gly Val
20 25 30

Arg Ser Val Thr Ile Val Tyr Leu Leu Asn Ile Ala Ile Ala Asp Leu
35 40 45

Leu Phe Ala Leu Thr Leu Pro Ile Trp Ala Ala Ser Lys Val Asn Gly
50 55 60

Trp Ile Phe Gly Thr Phe Leu Cys Lys Trp Ser Leu Leu Lys Glu Val
65 70 75 80

Asn Phe Tyr Ser Gly Ile Leu Leu Leu Ala Cys Ile Ser Val Asp Arg
85 90 95

Tyr Leu Ala Ile Val Arg Ala Thr Arg Thr Leu Thr Gln Lys Arg His
100 105 110

Leu Val Lys Phe Ile Cys Leu Ser Ile Trp Gly Leu Ser Leu Leu Leu
115 120 125

Ala Leu Pro Val Leu Leu Phe Arg Arg Thr Val Tyr Ser Ser Asn Val
130 135 140

Ser Pro Ala Cys Tyr Glu Asp Met Gly Asn Asn Tyr Ala Asn Trp Arg
145 150 155 160

Met Leu Leu Pro Ile Leu Pro Gln Ser Phe Gly Phe Ile Val Pro Leu
165 170 175

Leu Ile Met Leu Tyr Cys Tyr Gly Phe Thr Leu Arg Thr Leu Phe Lys
180 185 190

Ala Ile Met Gly Gln Lys His Arg Ala Met Arg Val Ile Phe Ala Val
195 200 205

Val Leu Ile Phe Leu Leu Cys Trp Leu Pro Tyr Asn Leu Val Leu Ile
210 215 220

Ala Asp Thr Leu Met Arg Thr Gln Val Ile Gln Glu Thr Cys Glu Arg
225 230 235 240

Arg Asn His Ile Asp Arg Ala Ile Asp Ala Thr Glu Ile Leu Gly Ile
245 250 255

Leu His Ser Cys Leu Asn Pro Leu Ile Tyr Ala Phe Ile Gly Gln Lys
260 265 270

Phe Arg His Gly Leu Leu Lys Ile Leu Ala Ile His Gly Leu Ile Ser
275 280 285

Lys Asp Ser Leu Pro Lys Asp Ser Arg Pro Ser Phe Val Gly Ser Ser
290 295 300

Ser Gly His Thr Ser Thr Thr Leu
305 310

(2) INFORMATION FOR SEQ ID NO:39:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 326 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:39:

Leu Phe Pro Ile Val Tyr Ser Ile Ile Phe Val Leu Gly Ile Ile Ala
1 5 10 15

Asn Gly Tyr Val Leu Trp Val Phe Ala Arg Leu Tyr Pro Ser Lys Lys
20 25 30

Asn Glu Ile Lys Ile Phe Met Val Asn Leu Thr Val Ala Asp Leu Leu
35 40 45

Phe Leu Ile Thr Leu Pro Leu Trp Ile Val Tyr Tyr Ser Asn Gln Gly
50 55 60

Asn Trp Phe Leu Pro Lys Phe Leu Cys Asn Leu Ala Gly Cys Leu Phe
65 70 75 80

Phe Ile Asn Thr Tyr Cys Ser Val Ala Phe Leu Gly Val Ile Thr Tyr
85 90 95

Asn Arg Phe Gln Ala Val Lys Tyr Pro Ile Lys Thr Ala Gln Ala Thr
100 105 110

Thr Arg Lys Arg Gly Ile Ala Leu Ser Leu Val Ile Trp Val Ala Ile
115 120 125

Val Ala Ala Ala Ser Tyr Phe Leu Val Met Met Asp Ser Thr Asn Val
130 135 140

Val Ser Asn Lys Ala Gly Ser Gly Asn Ile Thr Arg Cys Phe Glu Arg
145 150 155 160

Tyr Glu Lys Gly Ser Lys Pro Val Leu Ile Ile His Ile Cys Ile Val
165 170 175

Leu Gly Phe Phe Ile Val Phe Leu Leu Ile Leu Phe Cys Asn Leu Val
180 185 190

Ile Ile His Thr Leu Leu Arg Gly Pro Val Lys Gln Gln Arg Asn Ala
195 200 205

Glu Val Arg Arg Arg Ala Leu Trp Met Val Cys Thr Val Ile Ala Val
210 215 220

Phe Val Ile Cys Phe Val Pro His His Met Val Gln Leu Pro Trp Thr
225 230 235 240

Leu Ala Glu Leu Gly Met Trp Pro Ser Ser Asn His Gln Ala Ile Asn
245 250 255

Asp Ala His Gln Val Thr Leu Cys Leu Leu Ser Thr Asn Cys Val Leu
260 265 270

Asp Pro Val Ile Tyr Cys Phe Leu Thr Lys Lys Phe Arg Lys His Leu
275 280 285

Ser Glu Lys Leu Asn Ile Met Arg Ser Ser Gln Lys Cys Ser Arg Val
290 295 300

Thr Arg Asp Thr Gly Thr Glu Met Ala Ile Pro Ile Asn His Thr Pro
305 310 315 320

Val Asn Pro Ile Lys Asn

325

(2) INFORMATION FOR SEQ ID NO:40:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 333 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:40:

Tyr Ile Asn Thr Ile Val Ser Cys Leu Val Phe Val Leu Gly Ile Ile
1 5 10 15

Gly Asn Ser Thr Leu Leu Arg Ile Ile Tyr Lys Asn Lys Cys Met Arg
20 25 30

Asn Gly Pro Asn Ile Leu Ile Ala Ser Ile Ala Leu Gly Asp Leu Leu
35 40 45

His Ile Ile Ile Asp Ile Pro Ile Met Ala Tyr Lys Leu Ile Ala Gly
50 55 60

Asp Trp Pro Phe Ala Cys Lys Leu Phe Pro Phe Leu Gln Lys Ser Ser
65 70 75 80

Val Gly Ile Thr Val Leu Asn Leu Cys Ala Leu Ser Val Asp Arg Tyr
85 90 95

Arg Ala Val Ala Ser Trp Ser Arg Val Gln Gly Ile Gly Ile Pro Leu
100 105 110

Val Thr Ala Ile Glu Ile Val Ser Ile Trp Ile Leu Ser Phe Ile Leu
115 120 125

Ala Ile Pro Glu Ala Ile Gly Phe Trp Met Val Pro Phe Glu Tyr Lys
130 135 140

Gly Ala Gln His Arg Thr Cys Met Leu Asn Ala Thr Ser Lys Leu Phe
145 150 155 160

Tyr Gln Asp Val Lys Asp Trp Trp Leu Phe Gly Phe Tyr Phe Leu Leu
165 170 175

Val Cys Thr Ala Ile Phe Tyr Thr Leu Met Thr Cys Glu Met Leu Asn
180 185 190

Arg Arg Asn Gly Ser Leu Arg Ile Ala Leu Ser Glu His Leu Lys Gln
195 200 205

Arg Arg Glu Val Ala Lys Thr Val Phe Cys Leu Val Val Ile Phe Ala
210 215 220

Leu Cys Trp Phe Pro Leu His Leu Ser Arg Ile Leu Lys Lys Thr Val
225 230 235 240

Tyr Asp Glu Met Asp Thr Asn Arg Cys Glu Leu Leu Ser Phe Leu Leu
245 250 255

Leu Met Tyr Ile Gly Ile Asn Thr Ala Thr Met Ser Cys Ile Asn Pro
260 265 270

Ile Ala Leu Tyr Phe Val Ser Lys Lys Phe Lys Asn Cys Phe Gln Ser
275 280 285

Cys Leu Cys Cys Cys Cys Tyr Gln Ser Lys Ser Ile Met Thr Ser Val
290 295 300

Pro Met Gln Gly Thr Ser Ile Gln Trp Lys Asn His Glu Gln Asn Asn
305 310 315 320

His Asn Thr Glu Arg Ser Ser His Lys Asp Ser Ile Asn
325 330

(2) INFORMATION FOR SEQ ID NO:41:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 350 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:41:
Leu Ile Ala Ser Pro Trp Phe Ala Ala Ser Phe Cys Val Val Gly Leu
1 5 10 15

Ala Ser Asn Leu Leu Ala Leu Ser Val Leu Ala Gly Ala Arg Gln Ser
20 25 30

Ser Ser His Thr Arg Ser Ser Phe Leu Thr Phe Leu Cys Gly Leu Val
35 40 45

Leu Thr Leu Asp Phe Leu Gly Leu Leu Val Thr Gly Thr Ile Val Val
50 55 60

Ser Gln His Ala Ala Leu Phe Glu Trp His Ala Val Asp Pro Gly Cys
65 70 75 80

Arg Leu Cys Arg Leu Val Pro Phe Ile Gln Lys Ala Ser Val Gly Ile
85 90 95

Thr Val Leu Ser Leu Cys Ala Leu Ser Ile Asp Arg Tyr Arg Ala Val
100 105 110

Ala Ser Trp Ser Arg Ile Lys Gly Ile Gly Val Pro Lys Trp Thr Ala
115 120 125

Val Glu Ile Val Leu Ile Trp Val Val Ser Val Val Leu Ala Val Pro
130 135 140

Glu Ala Ile Gly Phe Asp Thr Thr Ser Asp Tyr Lys Gly Lys Pro Leu
145 150 155 160

Arg Val Cys Met Leu Asn Pro Phe Gln Lys Thr Ala Phe Met Phe Tyr
165 170 175

Lys Thr Ala Ala Lys Asp Trp Trp Leu Phe Ala Phe Tyr Phe Cys Leu
180 185 190

Pro Leu Ala Ile Thr Ala Ile Phe Tyr Thr Leu Met Thr Cys Glu Met
195 200 205

Leu Arg Lys Lys Ser Gly Met Gln Ile Ala Leu Asn Asp His Leu Lys
210 215 220

Gln Arg Arg Glu Val Ala Lys Thr Val Phe Cys Leu Val Leu Val Phe
225 230 235 240

Ala Leu Cys Trp Leu Pro Leu His Leu Ser Arg Ile Leu Lys Leu Thr
245 250 255

Leu Tyr Asp Gln Ser Asn Pro Gln Arg Cys Glu Leu Leu Ser Phe Leu
260 265 270

Leu Val Leu Asp Tyr Ile Gly Ile Asn Met Ala Ser Ile Asn Ser Cys

275 280 285

Ile Asn Pro Ile Ala Leu Tyr Leu Val Ser Lys Arg Phe Lys Asn Cys
290 295 300

Phe Lys Ser Cys Leu Cys Cys Trp Cys Gln Thr Phe Glu Glu Lys Gln
305 310 315 320

Ser Leu Glu Glu Lys Gln Ser Cys Leu Lys Phe Lys Ala Asn Asp His
325 330 335

Gly Tyr Asp Asn Phe Arg Ser Ser Asn Lys Tyr Ser Ser Ser
340 345 350

(2) INFORMATION FOR SEQ ID NO:42:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 328 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:42:
Ile Tyr Val Ile Pro Ala Val Tyr Gly Leu Ile Ile Val Ile Gly Leu
1 5 10 15
Ile Gly Asn Ile Thr Leu Ile Lys Ile Phe Cys Thr Val Lys Ser Leu
20 25 30

Asn Leu Phe Ile Ser Ser Ile Ala Leu Gly Asp Leu Leu Leu Leu Val
35 40 45

Thr Ile Cys Ala Pro Val Asp Ala Ser Lys Tyr Ile Ala Asp Arg Trp
50 55 60

Leu Phe Gly Arg Ile Gly Cys Lys Leu Ile Pro Phe Ile Gln Leu Thr
65 70 75 80

Ser Val Gly Val Ser Val Phe Thr Leu Thr Ala Leu Ser Ala Asp Arg
85 90 95

Tyr Lys Ala Ile Val Arg Pro Thr Cys Ile Gln Ala Ser Leu Ile Cys
100 105 110

Leu Lys Ala Ala Leu Ile Trp Ile Val Ser Leu Leu Ala Ile Pro Glu
115 120 125

Ala Val Phe Ser Asp Leu His Pro Phe His Val Lys Asp Thr Asn Gln
130 135 140

Thr Phe Ile Ser Cys Ala Pro Tyr Pro His Ser Asn Glu Leu His Pro
145 150 155 160

Lys Ile His Ser Met Ala Ser Phe Leu Val Phe Tyr Val Ile Pro Leu
165 170 175

Ala Ile Ile Ser Val Tyr Tyr Tyr Phe Ile Ala Arg Asn Leu Ile Gln
180 185 190

Ser Ala Tyr Asn Leu Pro Val Glu Gly Asn Ile His Val Lys Lys Gln
195 200 205

Ile Glu Ser Arg Lys Arg Leu Ala Lys Thr Val Leu Val Phe Val Gly
210 215 220

Leu Phe Ala Phe Cys Trp Leu Pro Asn His Val Ile Tyr Leu Tyr Arg
225 230 235 240

Ser Tyr His Tyr Ser Glu Val Asp Thr Ser Met Leu His Phe Val Thr
245 250 255

Ser Ile Cys Ala Arg Leu Leu Ala Pro Thr Asn Ser Cys Val Asn Pro
260 265 270

Phe Ala Leu Tyr Leu Leu Ser Lys Ser Phe Arg Gln Phe Asn Thr Gln
275 280 285

Leu Leu Cys Cys Gln Pro Gly Leu Ser His Ser Thr Gly Arg Ser Leu
290 295 300

Ser Phe Lys Ser Thr Asn Pro Ser Ala Thr Phe Ser Leu Ile Asn Arg
305 310 315 320

Asn Ile Cys His Glu Gly Tyr Val
325

(2) INFORMATION FOR SEQ ID NO:43:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 345 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:43:
Cys Val Ile Pro Ser Ser Leu Tyr Leu Ile Ile Ile Ser Val Gly Leu
1 5 10 15

Leu Gly Asn Ile Met Leu Val Lys Ile Phe Leu Thr Asn Ser Thr Met
20 25 30

Arg Ser Val Pro Asn Ile Phe Ile Ser Asn Ile Ala Ala Gly Asp Leu
35 40 45

Leu Leu Leu Leu Thr Cys Val Pro Val Asp Ala Ser Arg Tyr Phe Phe
50 55 60

Asp Glu Trp Val Phe Gly Lys Leu Ile Gly Cys Lys Leu Ile Pro Ala
65 70 75 80

Ile Gln Leu Thr Ser Val Gly Val Ser Val Pro Thr Leu Thr Ala Leu
85 90 95

Ser Ala Asp Arg Tyr Arg Ala Ile Val Asn Pro Met Asp Met Thr Ser
100 105 110

Gly Val Val Leu Trp Thr Ser Val Ala Val Gly Ile Trp Val Val Ser
115 120 125

Val Leu Leu Ala Val Pro Glu Ala Val Phe Ser Glu Val Ala Arg Ile
130 135 140

Gly Ser Ser Asp Asn Ser Ser Phe Thr Ala Cys Ile Pro Tyr Pro Gln
145 150 155 160

Thr Asp Glu Leu His Pro Lys Ile His Ser Val Leu Ile Phe Leu Val
165 170 175

Tyr Phe Leu Ile Pro Leu Val Ile Ile Ser Ile Tyr Tyr Tyr His Ile
180 185 190

Ala Lys Thr Leu Ile Arg Ser Ala His Asn Leu Pro Gly Glu Tyr Asn
195 200 205

Glu His Thr Lys Lys Gln Met Glu Thr Arg Lys Arg Leu Ala Lys Ile

```
    210                 215                 220

Val Leu Val Phe Val Gly Cys Phe Val Phe Cys Trp Phe Pro Asn His
225                 230                 235                 240

Ile Leu Tyr Leu Tyr Arg Ser Phe Asn Tyr Lys Glu Ile Asp Pro Ser
                245                 250                 255

Leu Gly Thr Cys Val Thr Leu Val Ala Arg Val Leu Ser Phe Ser Asn
            260                 265                 270

Ser Cys Val Asn Pro Phe Ala Leu Tyr Leu Leu Ser Glu Ser Phe Arg
        275                 280                 285

Lys His Phe Ser Asn Gln Leu Cys Cys Gly Gln Lys Ser Tyr Pro Glu
    290                 295                 300

Arg Ser Thr Ser Tyr Leu Leu Ser Ser Ser Ala Val Trp Arg Ser Leu
305                 310                 315                 320

Lys Ser Asn Ala Lys Asn Val Val Thr Asn Ser Val Leu Ile Asn Gly
                325                 330                 335

His Ser Thr Lys Gln Glu Ile Ala Leu
            340                 345
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(2) INFORMATION FOR SEQ ID NO:44:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 316 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:44:

```
Tyr Thr Leu Ser Phe Ile Tyr Ile Phe Ile Phe Val Ile Cys Glx Leu
1               5                   10                  15

Leu Ala Asn Ser Val Val Val Trp Val Asn Ile Gln Ala Lys Thr Thr
            20                  25                  30

Gly Tyr Asp Thr His Cys Tyr Ile Leu Asn Leu Ala Ile Ala Asp Leu
        35                  40                  45

Trp Trp Leu Thr Ile Pro Val Trp Trp Ser Leu Val Gln His Asn Gln
    50                  55                  60

Trp Pro Met Gly Glu Leu Thr Cys Lys Val Thr His Leu Ile Phe Ser
65                  70                  75                  80

Ile Asn Leu Phe Ser Gly Ile Phe Phe Leu Thr Cys Met Ser Val Asp
                85                  90                  95

Arg Tyr Leu Ser Ile Thr Tyr Phe Thr Asn Thr Pro Ser Ser Arg Lys
            100                 105                 110

Lys Met Val Arg Arg Ala Val Cys Ile Leu Val Trp Leu Leu Ala Phe
        115                 120                 125

Cys Val Ser Leu Pro Asp Thr Tyr Tyr Leu Lys Thr Val Thr Ser Ala
    130                 135                 140

Ser Asn Asn Glu Thr Tyr Cys Arg Ser Phe Tyr Pro Glu His Ser Ile
145                 150                 155                 160

Lys Glu Trp Leu Ile Ser Leu Leu Val Ser Val Val Leu Ile Gly Phe
                165                 170                 175
```

Ala Val Pro Phe Ser Ile Ile Ala Val Phe Tyr Phe Ser Leu Ile Ala
180 185 190

Arg Ala Ile Ser Ala Ser Ser Asp Gln Glu Lys His Ser Ser Arg Lys
195 200 205

Ile Ile Phe Ser Tyr Val Val Val Phe Leu Val Cys Trp Leu Pro Tyr
210 215 220

His Val Ala Val Leu Leu Asp Ile Phe Ser Ile Leu His Tyr Ile Pro
225 230 235 240

Phe Thr Cys Arg Leu Glu His Ala Leu Phe Thr Ala Leu His Val Thr
245 250 255

Gln Cys Leu Ser Leu Val His Cys Cys Val Asn Pro Val Leu Tyr Ser
260 265 270

Phe Ile Asn Arg Asn Tyr Arg Tyr Glu Ile Asn Trp Ile Phe Lys Tyr
275 280 285

Ser Ala Lys Thr Gly Leu Thr Lys Leu Ile Asp Ala Ser Arg Val Ser
290 295 300

Glx Thr Glu Tyr Ser Ala Leu Glu Gln Asn Ala Lys
305 310 315

(2) INFORMATION FOR SEQ ID NO:45:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 353 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:45:
Lys Val Leu Val Thr Ala Ile Tyr Leu Ala Leu Phe Val Val Gly Thr
1 5 10 15

Val Gly Asn Ser Val Thr Ala Phe Thr Leu Ala Arg Lys Lys Ser Leu
20 25 30

Gln Ser Leu Gln Ser Thr Val His Tyr His Leu Ser Ser Leu Ala Leu
35 40 45

Ser Asp Leu Leu Ile Leu Leu Trp Val Glu Leu Tyr Asn Phe Ile Trp
50 55 60

His His Pro Trp Ala Phe Gly Asp Ala Gly Cys Arg Gly Tyr Tyr Phe
65 70 75 80

Leu Arg Asp Ala Cys Thr Tyr Ala Thr Ala Leu Asn Val Ala Ser Leu
85 90 95

Ser Val Glu Arg Tyr Leu Ala Ile Cys His Pro Phe Lys Ala Lys Thr
100 105 110

Leu Met Ser Arg Ser Arg Thr Lys Lys Phe Ile Ser Ala Ile Trp Leu
115 120 125

Ala Ser Ala Leu Leu Ala Ile Pro Met Leu Phe Thr Leu Gly Leu Gln
130 135 140

Asn Arg Ser Gly Asp Gly Thr His Pro Gly Gly Leu Val Cys Thr Pro
145 150 155 160

Ile Val Asp Thr Ala Thr Val Lys Val Val Ile Gln Val Asn Thr Phe

165 170 175

Met Ser Phe Leu Phe Pro Met Leu Val Ile Ser Ile Leu Asn Thr Val
180 185 190

Ile Ala Asn Lys Leu Thr Val Met Val His Gln Ala Ala Glu Gln Gly
195 200 205

Arg Val Cys Thr Val Gly Thr His Asn Gly Leu Glu His Ser Thr Phe
210 215 220

Asn Met Arg Ile Glu Pro Gly Arg Val Gln Ala Leu Arg His Gly Val
225 230 235 240

Leu Val Leu Arg Ala Val Val Ile Ala Phe Val Val Cys Trp Leu Pro
245 250 255

Tyr Leu Cys Tyr Ile Ser Asp Glu Gln Trp Arg Thr Phe Leu Phe Asp
260 265 270

Phe Tyr His Tyr Phe Tyr Met Leu Thr Asn Ala Leu Phe Tyr Val Ser
275 280 285

Ser Ala Ile Asn Pro Ile Leu Tyr Asn Leu Val Ser Ala Asn Phe Arg
290 295 300

Gln Val Phe Leu Ser Thr Leu Ala Cys Leu Phe Cys Pro Gly Trp Pro
305 310 315 320

Leu Ile Arg Arg Lys Lys Arg Pro Thr Phe Ser Arg Lys Pro Asn Ser
325 330 335

Met Ser Ser Asn His Ala Phe Ser Thr Ser Ala Thr Arg Phe Thr Leu
340 345 350

Tyr

(2) INFORMATION FOR SEQ ID NO:46:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 316 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:46:
Ala Ile Gln Ala Pro Phe Leu Trp Val Leu Phe Leu Leu Ala Ala Leu
1 5 10 15

Glu Asn Ile Phe Val Leu Ser Val Phe Cys Leu His Lys Thr Asn Cys
20 25 30

Thr Val Ala Glu Ile Tyr Leu Gly Asn Ile Ala Ser Ala Asp Leu Ile
35 40 45

Ile Ala Cys Gly Leu Pro Phe Trp Ala Ile Thr Ile Ala Asn Asn Phe
50 55 60

Asp Trp Leu Phe Gly Glu Val Leu Cys Arg Val Val Asn Leu Tyr Met
65 70 75 80

Asn Leu Tyr Ser Ser Ile Cys Phe Leu Val Ser Ile Asp Arg Tyr Leu
85 90 95

Ala Leu Val Lys Thr Met Ser Asn Leu Arg Trp Ala Lys Leu Tyr Ser
100 105 110

Leu Val Ile Trp Ser Cys Thr Leu Leu Leu Ser Ser Pro Met Leu Val
115 120 125

Phe Arg Thr Met Tyr Arg Glu Glu Gly His Asn Val Thr Cys Val Ile
130 135 140

Val Tyr Pro Ser Arg Ser Trp Glu Val Phe Leu Leu Asn Leu Val Gly
145 150 155 160

Phe Leu Leu Pro Leu Ser Ile Ile Thr Phe Cys Thr Val Arg Ile Met
165 170 175

Val Leu Arg Asn Asn Glu Met Lys Lys Phe Lys Glu Val Gln Thr Glu
180 185 190

Lys Lys Ala Thr Val Leu Val Ile Ala Val Leu Gly Leu Phe Val Leu
195 200 205

Cys Trp Phe Pro Phe Gln Ile Ser Thr Phe Leu Asp Thr Leu Leu Arg
210 215 220

Leu Gly Val Leu Ser Gly Cys Trp Asn Glu Arg Ala Val Asp Ile Val
225 230 235 240

Arg Gln Ile Ser Ser Tyr Val Ala Tyr Ser Asn Ser Cys Leu Asn Pro
245 250 255

Leu Val Tyr Val Ile Val Gly Lys Arg Phe Arg Lys Lys Ser Arg Glu
260 265 270

Val Tyr Gln Ala Ile Cys Arg Lys Gly Gly Cys Met Gly Glu Ser Val
275 280 285

Leu Asn Ser Met Gly Thr Leu Arg Thr Ser Ile Ser Val Asp Arg Gln
290 295 300

Ile His Lys Leu Gln Asp Trp Ala Gly Asn Lys Gln
305 310 315

(2) INFORMATION FOR SEQ ID NO:47:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 347 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:47:
Ile Leu Leu Val Val Ile Ile Cys Gly Leu Gly Ile Val Gly Asn Ile
1 5 10 15

Met Val Val Leu Val Val Met Arg Thr Thr Pro Thr Asn Cys Tyr Leu
20 25 30

Val Ser Ile Ala Val Ala Asp Leu Met Val Leu Val Ala Ala Gly Leu
35 40 45

Pro Asn Ile Thr Asp Ser Ile Tyr Gly Ser Trp Val Tyr Gly Tyr Val
50 55 60

Gly Cys Leu Cys Ile Thr Tyr Leu Gln Tyr Leu Gly Ile Asn Ala Ser
65 70 75 80

Ser Cys Ser Ile Thr Ala Phe Thr Ile Glu Arg Tyr Ile Ala Ile Cys
85 90 95

His Pro Ile Lys Ala Gln Phe Leu Cys Thr Phe Ser Arg Ala Lys Lys

100 105 110

Ile Ile Ile Phe Val Trp Ala Phe Thr Ser Ile Tyr Leu Phe Leu Leu
115 120 125

Asp Ile Asn Ile Ser Thr Tyr Lys Asn Ala Val Val Val Ser Cys Gly
130 135 140

Tyr Lys Ile Ser Arg Asn Tyr Tyr Ser Pro Ile Tyr Leu Met Asp Phe
145 150 155 160

Gly Val Phe Tyr Val Val Pro Leu Ile Ala Thr Val Leu Tyr Gly Phe
165 170 175

Ile Ala Arg Ile Leu Phe Leu Asn Pro Ile Pro Ser Asp Pro Lys Glu
180 185 190

Asn Ser Lys Met Trp Lys Asn Asp Ser Ile His Gln Asn Lys Asn Leu
195 200 205

Asn Leu Asn Ala Ser Ser Arg Lys Gln Val Thr Ile Asn Leu Ala Val
210 215 220

Val Val Ile Leu Phe Ala Leu Leu Trp Asn Thr Tyr Arg Thr Leu Val
225 230 235 240

Val Val Asn Ser Phe Leu Ser Ser Pro Phe Gln Glu Asn Trp Lys Leu
245 250 255

Leu Lys Cys Arg Ile Cys Ile Tyr Leu Asn Ser Ala Ile Asn Pro Val
260 265 270

Ile Tyr Asn Ile Met Ser Gln Lys Arg Phe Ala Ala Phe Arg Lys Leu
275 280 285

Cys Asn Cys Lys Gln Lys Pro Thr Glu Lys Ala Ala Asn Tyr Ser Val
290 295 300

Ala Leu Asn Tyr Ser Val Ile Lys Glu Ser Asp Arg Phe Ser Thr Glu
305 310 315 320

Leu Glu Asp Ile Thr Val Thr Asp Thr Tyr Val Ser Thr Thr Lys Val
325 330 335

Ser Phe Asp Asp Thr Cys Ile Ala Ser Glu Asn
340 345

(2) INFORMATION FOR SEQ ID NO:48:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 341 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:48:
Leu Ala Leu Trp Ala Thr Ala Tyr Leu Ala Leu Val Leu Val Ala Val
1 5 10 15

Thr Gly Asn Ala Ile Val Ile Trp Ile Ile Leu Ala His Arg Arg Met
20 25 30

Arg Thr Val Thr Asn Tyr Phe Ile Val Asn Ile Ala Leu Ala Asp Leu
35 40 45

Leu Asn Ala Ala Phe Asn Phe Val Tyr Ala Ser His Asn Ile Trp Tyr

50 55 60

Phe Gly Arg Ala Phe Cys Tyr Phe Gln Asn Leu Phe Pro Ile Thr Ala
65 70 75 80

Met Phe Val Ser Ile Tyr Ser Met Thr Ala Ile Ala Ala Asp Arg Tyr
85 90 95

Met Ala Ile Val His Pro Phe Gln Pro Arg Leu Ser Ala Pro Ser Thr
100 105 110

Lys Ala Val Ile Ala Gly Ile Trp Leu Val Ala Ile Lys Leu Ala Phe
115 120 125

Pro Gln Cys Phe Tyr Ser Thr Val Thr Met Gln Gly Ala Thr Lys Cys
130 135 140

Val Val Ala Trp Pro Glu Asp Ser Gly Gly Lys Thr Leu Leu Leu Tyr
145 150 155 160

His Leu Val Val Ile Ala Leu Ile Tyr Phe Leu Pro Ile Ala Leu Ala
165 170 175

Tyr Ser Val Ile Gly Leu Thr Leu Trp Arg Arg Ala Val Pro Gly His
180 185 190

Gln Ala His Gly Ala Asn Leu Arg His Leu Gln Ala Lys Lys Lys Phe
195 200 205

Val Lys Thr Met Val Leu Val Val Val Thr Phe Ala Ile Cys Trp Leu
210 215 220

Pro Tyr His Leu Tyr Phe Ile Leu Gly Ser Phe Gln Glu Asp Ile Tyr
225 230 235 240

Cys His Lys Phe Ile Gln Gln Val Tyr Leu Ala Leu Phe Trp Leu Ala
245 250 255

Met Ser Ser Thr Met Tyr Asn Pro Ile Ile Tyr Cys Cys Leu Asn His
260 265 270

Arg Phe Arg Ser Gly Phe Arg Leu Ala Phe Arg Cys Cys Pro Trp Val
275 280 285

Thr Pro Thr Lys Glu Asp Lys Leu Glu Leu Thr Pro Thr Thr Ser Leu
290 295 300

Ser Thr Arg Val Asn Arg Cys His Thr Lys Glu Thr Leu Phe Met Ala
305 310 315 320

Gly Asp Thr Ala Pro Ser Glu Ala Thr Ser Gly Glu Ala Gly Arg Pro
325 330 335

Gln Asp Gly Ser Gly
340

(2) INFORMATION FOR SEQ ID NO:49:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 340 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:49:
Ile Val Leu Trp Ala Ala Ala Tyr Thr Val Ile Val Val Arg Ser Val
1 5 10 15

Val Gly Asn Val Val Val Ile Trp Ile Ile Leu Ala His Lys Arg Met
20 25 30

Arg Thr Val Thr Asn Tyr Phe Leu Val Asn Ile Ala Phe Ala Phe Ala
35 40 45

Leu Asn Thr Trp Asn Phe Thr Tyr Ala Val His Asn Val Trp Tyr Tyr
50 55 60

Gly Leu Phe Tyr Cys Lys Phe His Asn Phe Phe Pro Ile Ala Ala Leu
65 70 75 80

Phe Ala Ser Ile Tyr Ser Met Thr Ala Val Ala Phe Asp Arg Tyr Leu
85 90 95

Ile Ile His Pro Leu Gln Pro Arg Leu Ser Ala Thr Ala Thr Lys Val
100 105 110

Val Ile Phe Val Ile Trp Val Ile Ala Leu Leu Leu Ala Ser Pro Gln
115 120 125

Gly Tyr Tyr Ser Thr Thr Glu Leu Ser Arg Val Val Cys Met Ile Glu
130 135 140

Trp Pro Glu His Pro Asn Arg Thr Tyr Glu Lys Ala Tyr His Ile Cys
145 150 155 160

Val Thr Val Leu Ile Tyr Phe Leu Pro Leu Leu Val Ile Gly Tyr Ala
165 170 175

Tyr Thr Val Val Gly Ile Thr Leu Trp Ala Ser Glu Ile Pro Gly Asp
180 185 190

Ser Ser Asp Arg Tyr His Glu Gln Val Ser Ala Lys Arg Lys Val Val
195 200 205

Lys Met Ile Cys Val Val Val Cys Thr Phe Ala Ile Cys Trp Leu Pro
210 215 220

Phe His Val Phe Phe Leu Leu Pro Tyr Ile Asn Pro Asp Leu Tyr Leu
225 230 235 240

Lys Lys Phe Ile Gln Gln Val Tyr Ile Ala Ser Met Trp Leu Ala Met
245 250 255

Ser Ser Thr Met Tyr Asn Pro Ile Ile Tyr Cys Cys Leu Asn Asp Arg
260 265 270

Phe Arg Leu Gly Phe Lys His Ala Phe Arg Cys Cys Pro Phe Ile Ser
275 280 285

Ala Gly Asp Tyr Glu Gly Leu Glu Met Ile Lys Ser Thr Arg Tyr Leu
290 295 300

Gln Thr Leu Ser Ser Val Tyr Lys Val Ser Arg Leu Glu Thr Thr Ile
305 310 315 320

Ser Thr Val Val Gly Ala His Glu Glu Glu Pro Glu Glu Gly Pro Lys
325 330 335

Ala Thr Pro Ser
340

(2) INFORMATION FOR SEQ ID NO:50:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 336 amino acids
(B) TYPE: amino acid

(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:50:

Ile Ala Leu Trp Ser Leu Ala Tyr Gly Leu Val Val Ala Val Ala Val
1 5 10 15

Phe Gly Asn Leu Ile Val Ile Trp Ile Ile Leu Ala His Lys Arg Met
20 25 30

Arg Thr Val Thr Asn Tyr Phe Leu Val Asn Leu Ala Phe Ser Asp Ala
35 40 45

Ser Val Ala Ala Phe Asn Thr Leu Ile Asn Phe Ile Tyr Gly Leu His
50 55 60

Ser Glu Trp Tyr Phe Gly Ala Asn Tyr Cys Arg Phe Gln Asn Phe Phe
65 70 75 80

Pro Ile Thr Ala Val Phe Ala Ser Ile Tyr Ser Met Ala Ile Ala Val
85 90 95

Asp Arg Tyr Met Ala Ile Ile Asp Pro Leu Lys Pro Arg Leu Ser Ala
100 105 110

Thr Ala Thr Lys Ile Val Ile Gly Ser Ile Trp Ile Leu Ala Phe Leu
115 120 125

Leu Ala Phe Pro Gln Cys Leu Tyr Ser Lys Ile Leu Gly Arg Thr Leu
130 135 140

Cys Tyr Val Trp Pro Glu Gly Pro Lys Gln His Phe Thr Tyr His Ile
145 150 155 160

Ile Val Ile Ile Leu Val Tyr Cys Phe Pro Leu Leu Ile Leu Thr Tyr
165 170 175

Thr Ile Val Gly Ile Thr Leu Trp Gly Gly Glu Ile Pro Gly Asp Thr
180 185 190

Cys Asp Lys Tyr His Glu Gln Leu Lys Ala Lys Arg Lys Val Val Met
195 200 205

Asn Ile Val Val Val Thr Phe Ala Ile Cys Trp Leu Pro Tyr His Val
210 215 220

Tyr Phe Ile Leu Thr Ala Ile Tyr Gln Gln Leu Asn Arg Trp Lys Tyr
225 230 235 240

Ile Gln Gln Val Tyr Leu Ala Ser Phe Trp Leu Ala Met Ser Ser Thr
245 250 255

Met Tyr Asn Pro Ile Ile Tyr Cys Cys Leu Asn Lys Arg Phe Arg Ala
260 265 270

Gly Phe Lys Arg Ala Phe Arg Trp Cys Pro Phe Ile Gln Val Ser Ser
275 280 285

Tyr Asp Glu Leu Glu Leu Lys Thr Thr Arg Phe His Pro Thr Arg Gln
290 295 300

Ser Ser Leu Tyr Thr Val Ser Phe Met Ser Val Thr Val Leu Phe Asp
305 310 315 320

Pro Asn Asp Gly Asp Pro Thr Lys Ser Ser Arg Lys Lys Arg Ala Val
325 330 335

(2) INFORMATION FOR SEQ ID NO:51:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 325 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:51:

Met Ile Pro Thr Leu Tyr Ser Ile Ile Phe Val Val Gly Ile Phe Gly
1 5 10 15

Asn Ser Leu Val Val Ile Val Ile Tyr Phe Tyr Met Lys Leu Lys Thr
20 25 30

Tyr Ala Ser Val Phe Leu Leu Asn Leu Ala Leu Ala Asp Leu Cys Phe
35 40 45

Leu Leu Thr Leu Pro Leu Trp Ala Val Tyr Thr Leu Tyr Arg Trp Pro
50 55 60

Phe Gly Asn Tyr Leu Cys Lys Ile Ala Ser Ala Ser Val Ser Phe Asn
65 70 75 80

Leu Tyr Ala Ser Val Phe Leu Leu Thr Cys Leu Ser Ile Asp Arg Tyr
85 90 95

Leu Ala Ile Val His Pro Met Lys Ser Arg Leu Arg Arg Leu Val Ala
100 105 110

Lys Val Thr Cys Ile Ile Ile Trp Leu Leu Ala Gly Ile Ala Ser Leu
115 120 125

Pro Thr Ile Ile His Arg Asn Phe Phe Ile Glu Asn Thr Asn Ile Thr
130 135 140

Val Cys Ala Phe His Tyr Glu Ser Gln Asn Ser Thr Leu Pro Val Gly
145 150 155 160

Leu Gly Leu Thr Lys Asn Ile Leu Gly Phe Leu Phe Pro Phe Leu Ile
165 170 175

Ile Leu Thr Ser Tyr Thr Leu Ile Trp Lys Thr Leu Lys Lys Ala Tyr
180 185 190

Glu Ile Gln Lys Asn Lys Pro Arg Lys Asp Asp Ile Phe Lys Ile Ile
195 200 205

Ile Ala Ile Val Leu Phe Phe Phe Phe Ser Trp Val Pro His Asn Ile
210 215 220

Phe Thr Phe Met Val Leu Ile Gln Leu Gly Leu Ile Arg Asp Cys Lys
225 230 235 240

Ile Glu Asp Ile Val Asp Thr Ala Met Pro Ile Thr Ile Cys Leu Ala
245 250 255

Tyr Phe Gln Gln Asn Leu Asn Pro Leu Phe Tyr Gly Phe Leu Gly Lys
260 265 270

Lys Phe Lys Lys Tyr Phe Leu His Ala Leu Leu Lys Tyr Ile Pro Pro
275 280 285

Lys Ala Lys Ser His Ser Asn Leu Ser Thr Lys Met Ser Thr Leu Ser
290 295 300

Tyr Arg Pro Ser Glu Gln Gly Asn Ser Ser Thr Lys Lys Pro Ala Pro
305 310 315 320

Cys Ile Glu Val Glu
325

(2) INFORMATION FOR SEQ ID NO:52:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 282 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:52:
Ile Val His Trp Val Ile Met Ser Ile Ser Pro Val Gly Phe Val Glu
1 5 10 15

Asn Gly Ile Leu Leu Trp Phe Leu Cys Phe Phe Thr Val Tyr Thr His
20 25 30

Leu Ser Ile Ala Asp Ile Ser Leu Leu Phe Cys Ile Phe Ile Leu Ser
35 40 45

Ile Asp Tyr Ala Leu Asp Tyr Glu Leu Ser Ser Gly His Tyr Tyr Thr
50 55 60

Ile Val Thr Leu Ser Val Thr Phe Leu Phe Gly Tyr Asn Thr Gly Leu
65 70 75 80

Tyr Leu Leu Thr Ala Ile Ser Val Glu Arg Cys Leu Ser Val Leu Tyr
85 90 95

Pro Ile Trp Tyr Arg Cys His Arg Pro Lys Tyr Gln Ser Ala Leu Val
100 105 110

Cys Ala Leu Leu Trp Ala Leu Ser Cys Leu Val Thr Thr Met Tyr Val
115 120 125

Met Cys Ile Asp Arg Phe Glu Glu Ser His Ser Arg Asn Asp Cys Arg
130 135 140

Ala Val Ile Ile Phe Ile Ala Ile Leu Ser Phe Leu Val Phe Thr Pro
145 150 155 160

Ser Val Ser Ser Thr Ile Leu Val Val Lys Ile Arg Lys Asn Thr Trp
165 170 175

Ala Ser His Ser Ser Lys Leu Tyr Ile Val Ile Met Val Thr Ile Ile
180 185 190

Ile Phe Leu Ile Phe Ala Met Pro Met Arg Leu Leu Tyr Leu Leu Tyr
195 200 205

Tyr Glu Tyr Trp Ser Thr Phe Gly Asn Leu His His Ile Ser Leu Leu
210 215 220

Phe Ser Thr Ile Asn Ser Ser Ala Asn Pro Phe Ile Tyr Phe Phe Val
225 230 235 240

Gly Ser Ser Lys Lys Lys Arg Phe Lys Glu Ser Leu Lys Val Val Leu
245 250 255

Thr Arg Ala Phe Lys Asp Glu Met Gln Pro Arg Arg Gln Lys Asp Asn
260 265 270

Cys Asn Thr Val Thr Val Glu Thr Val Val

275 280

(2) INFORMATION FOR SEQ ID NO:53:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 332 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:53:

Tyr Asp Phe Leu Arg Val Leu Ile Trp Leu Ile Asn Ile Leu Ala Ile
1 5 10 15

Met Gly Asn Val Met Thr Leu Phe Val Leu Leu Thr Ser Arg Tyr Lys
20 25 30

Leu Thr Val Pro Arg Phe Ile Met Asn Leu Ser Phe Ala Asp Phe Cys
35 40 45

Met Leu Tyr Leu Leu Leu Ile Ala Ser Val Asp Ser Gln Thr Lys Gly
50 55 60

Gln Tyr Tyr Asn His Ala Ile Asp Trp Gln Thr Gly Ser Gly Cys Ser
65 70 75 80

Thr Ala Gly Phe Phe Thr Val Leu Ala Ser Glu Leu Ser Val Tyr Thr
85 90 95

Leu Thr Val Ile Thr Leu Glu Arg Trp His Thr Ile Thr Tyr Ala Ile
100 105 110

His Ile Asp Gln Lys Leu Arg Leu Arg His Ala Ile Leu Ile Met Leu
115 120 125

Gly Gly Trp Leu Phe Ser Ser Leu Ile Ala Met Leu Pro Leu Val Cys
130 135 140

Val Ser Asn Tyr Met Lys Val Ser Ile Cys Leu Pro Met Val Glu Thr
145 150 155 160

Thr Leu Ser Gln Val Tyr Ile Leu Thr Ile Leu Ile Leu Asn Val Val
165 170 175

Ala Phe Leu Ile Ile Cys Ala Cys Tyr Ile Lys Ile Tyr Phe Ala Val
180 185 19:

Arg Asn Pro Glu Ile Met Ala Thr Asn Lys Asp Thr Lys Ile Ala Leu
195 200 205

Ala Ile Leu Ile Phe Thr Asp Phe Thr Cys Met Pro Ile Ser Phe Phe
210 215 220

Ala Ile Ser Ala Ala Phe Lys Val Pro Leu Ile Val Thr Asn Ser Lys
225 230 235 240

Val Leu Leu Val Leu Phe Tyr Pro Ile Asn Ser Cys Ala Asn Pro Phe
245 250 255

Leu Tyr Ala Ile Phe Thr Lys Thr Phe Gln Arg Asp Phe Phe Ile Leu
260 265 270

Ser Lys Phe Cys Cys Lys Arg Arg Ala Asp Ile Tyr Arg Arg Lys Asp
275 280 285

Phe Ser Ala Tyr Thr Ser Asn Cys Lys Lys Gly Phe Thr Gly Ser Asn
290 295 300

Lys Pro Ser Gln Ser Thr Leu Lys Leu Ser Thr Leu His Cys Gln Gly
305 310 315 320

Thr Ala Leu Leu Asp Lys Arg Arg Tyr Thr Glu Cys
325 330

(2) INFORMATION FOR SEQ ID NO:54:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 336 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:54:

Tyr Lys Phe Leu Arg Ile Val Val Trp Phe Val Ser Leu Leu Ala Leu
1 5 10 15

Leu Gly Asn Val Phe Val Leu Leu Ile Leu Leu Thr Ser His Tyr Lys
20 25 30

Leu Asn Val Pro Arg Phe Ile Met Asn Ile Ala Phe Ala Asp Phe Cys
35 40 45

Met Met Tyr Leu Leu Leu Leu Ile Ala Ser Val Asp Leu Tyr Thr His Ser
50 55 60

Glu Tyr Tyr Asn His Ala Ile Asp Trp Gln Thr Gly Pro Gly Cys Asn
65 70 75 80

Thr Ala Gly Phe Phe Thr Val Phe Ala Ser Glu Leu Ser Val Tyr Thr
85 90 95

Leu Thr Val Ile Thr Leu Glu Arg Trp Tyr Ala Ile Thr Phe Ala Met
100 105 110

Arg Leu Asp Arg Lys Ile Arg Leu Arg His Ala Cys Ala Ile Met Val
115 120 125

Gly Gly Trp Val Cys Cys Phe Leu Leu Ala Leu Leu Pro Leu Val Gly
130 135 140

Ile Ser Ser Tyr Ala Lys Val Ser Ile Cys Leu Pro Met Thr Glu Thr
145 150 155 160

Pro Leu Ala Leu Ala Tyr Ile Val Phe Val Leu Thr Leu Asn Ile Val
165 170 175

Ala Phe Val Ile Val Cys Cys Cys Tyr Val Lys Ile Tyr Ile Thr Val
180 185 190

Arg Asn Pro Gln Tyr Asn Pro Gly Asp Lys Asp Thr Lys Ile Ala Lys
195 200 205

Arg Met Ala Val Leu Ile Phe Thr Asp Phe Ile Cys Met Ala Pro Ile
210 215 220

Ser Phe Tyr Ala Leu Ser Ala Ile Leu Asn Lys Pro Leu Ile Thr Val
225 230 235 240

Ser Asn Ser Lys Ile Leu Leu Val Leu Phe Tyr Pro Leu Asn Ser Cys
245 250 255

Ala Asn Pro Phe Leu Tyr Ala Ile Phe Thr Lys Ala Phe Gln Arg Asp
260 265 270

Val Phe Ile Leu Leu Ser Lys Phe Gly Ile Cys Lys Arg Gln Ala Gln
275 280 285

Ala Tyr Arg Gly Gln Arg Val Pro Pro Lys Asn Ser Thr Asp Ile Gln
290 295 300

Val Gln Lys Val Thr His Asp Met Arg Gln Gly Ala Leu Asn Met Glu
305 310 315 320

Asp Val Val Glu Leu Ile Glu Asn Ser His Leu Thr Pro Lys Lys Gln
325 330 335

(2) INFORMATION FOR SEQ ID NO:55:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 327 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:55:
Tyr Asn Ile Leu Arg Val Leu Ile Trp Phe Ile Ser Ile Leu Ala Ile
1 5 10 15

Thr Gly Asn Ile Ile Val Leu Val Ile Leu Thr Thr Ser Gln Tyr Lys
20 25 30

Leu Thr Val Pro Arg Phe Leu Met Asn Ile Ala Phe Ala Asp Leu Cys
35 40 45

Ile Gly Ile Tyr Leu Leu Leu Ile Ala Ser Val Asp Ile His Thr Lys
50 55 60

Ser Gln Tyr His Asn Tyr Ala Ile Asp Trp Gln Arg Gly Ala Gly Cys
65 70 75 80

Asp Ala Ala Gly Phe Phe Thr Val Phe Ala Ser Glu Leu Ser Val Tyr
85 90 95

Thr Leu Thr Ala Ile Thr Leu Glu Arg Trp His Thr Ile Thr His Ile
100 105 110

Met Gln Ile Asp Cys Lys Val Gln Leu Arg His Ala Ala Ser Val Met
115 120 125

Val Met Gly Trp Ile Phe Ala Phe Ala Ala Ala Leu Phe Pro Ile Phe
130 135 140

Gly Ile Ser Ser Tyr Met Lys Val Ser Ile Cys Leu Pro Leu Ile Asp
145 150 155 160

Ser Pro Leu Ser Gln Leu Tyr Val Met Ser Leu Leu Val Leu Asn Val
165 170 175

Leu Ala Phe Val Val Ile Cys Gly Cys Tyr Thr His Ile Tyr Leu Thr
180 185 190

Val Arg Asn Pro Asn Ile Val Ser Ser Ser Ser Asp Thr Arg Ile Ala
195 200 205

Lys Arg Met Leu Ile Phe Thr Asp Phe Leu Leu Pro Ile Ser Phe Phe
210 215 220

Ala Ile Ser Ala Ser Leu Lys Val Pro Leu Ile Thr Val Ser Lys Ala
225 230 235 240

Lys Ile Leu Leu Val Leu Phe His Pro Ile Asn Ser Cys Ala Asn Pro

245 250 255

Phe Leu Tyr Ala Ile Phe Thr Lys Asn Phe Arg Arg Asp Phe Phe Ile
260 265 270

Leu Leu Ser Lys Cys Gly Cys Tyr Glu Met Gln Ala Gln Ile Tyr Arg
275 280 285

Thr Glu Thr Ser Ser Thr Val His Asn Thr His Pro Arg Asn Gly His
290 295 300

Cys Ser Ser Ala Pro Arg Val Thr Ser Gly Ser Ser Arg Tyr Ile Leu
305 310 315 320

Val Pro Leu Ser Leu Gln Asn
325

(2) INFORMATION FOR SEQ ID NO:56:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 309 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:56:

Ser Met Leu Ala Ala Tyr Met Phe Leu Leu Ile Val Leu Gly Phe Pro
1 5 10 15

Ile Asn Phe Leu Thr Leu Tyr Val Thr Val Gln His Lys Lys Leu Arg
20 25 30

Thr Pro Ile Asn Tyr Ile Leu Leu Asn Leu Ala Val Ala Asp Leu Phe
35 40 45

Met Val Leu Gly Gly Phe Thr Ser Thr Leu Tyr Thr Ser Leu His Gly
50 55 60

Tyr Phe Val Phe Gly Pro Thr Gly Cys Asn Leu Glu Gly Phe Phe Ala
65 70 75 80

Thr Leu Gly Gly Glu Ile Ala Leu Trp Ser Leu Trp Leu Ala Ile Glu
85 90 95

Arg Tyr Val Val Val Cys Lys Pro Met Ser Asn Phe Arg Phe Gly Glu
100 105 110

Asn His Ala Ile Met Gly Val Ala Phe Thr Trp Val Met Ala Leu Ala
115 120 125

Cys Ala Ala Pro Pro Ile Ala Gly Trp Ser Arg Tyr Ile Pro Glu Gly
130 135 140

Leu Gln Cys Ser Cys Gly Ile Asp Tyr Tyr Thr Leu Lys Pro Glu Val
145 150 155 160

Asn Asn Glu Ser Phe Val Ile Tyr Met Phe Val Val His Phe Thr Ile
165 170 175

Pro Leu Ile Ile Phe Phe Cys Tyr Gly Gln Leu Val Phe Thr Val Lys
180 185 190

Glu Ala Ala Ala Gln Gln Gln Glu Ser Ala Thr Thr Gln Lys Ala Glu
195 200 205

Lys Glu Val Thr Arg Met Val Ile Ile Met Val Ile Ala Phe Leu Ile
210 215 220

Cys Trp Val Pro Tyr Ala Ser Val Ala Phe Tyr Ile Phe Thr His Gln
225 230 235 240

Gly Ser Asn Phe Gly Pro Ile Phe Met Arg Ile Pro Ala Phe Phe Ala
245 250 255

Lys Ser Ala Ala Ile Tyr Asn Pro Val Ile Tyr Ile Ile Phe Asn Lys
260 265 270

Gln Phe Arg Asn Cys Met Leu Gln Leu Ile Cys Cys Gly Lys Asn Pro
275 280 285

Leu Gly Asp Asp Glu Ala Ser Ala Thr Val Ser Lys Arg Glu Thr Ser
290 295 300

Gln Val Ala Pro Ala
305

(2) INFORMATION FOR SEQ ID NO:57:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 297 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:57:
Met Ile Phe Val Val Ile Ala Ser Val Phe Thr Asn Gly Leu Val Leu
1 5 10 15

Ala Ala Thr Met Lys Phe Lys Lys Leu Pro His Pro Ile Asn Trp Ile
20 25 30

Leu Val Asn Leu Ala Val Ala Asp Ile Ala Gly Thr Val Ile Ala Ser
35 40 45

Thr Ile Ser Val Val Asn Gln Val Tyr Gly Tyr Phe Val Leu Gly His
50 55 60

Pro Met Cys Val Leu Glu Gly Tyr Thr Val Ser Leu Cys Gly Ile Thr
65 70 75 80

Gly Leu Trp Ser Leu Ala Ile Ile Ser Trp Glu Arg Trp Met Val Val
85 90 95

Cys Lys Pro Phe Gly Asn Val Arg Phe Asp Ala Lys Ile Ala Ile Val
100 105 110

Gly Ile Ala Phe Ser Trp Ile Trp Ala Ala Val Trp Thr Ala Pro Pro
115 120 125

Ile Phe Gly Trp Ser Arg Tyr Trp Pro His Gly Leu Lys Thr Ser Cys
130 135 140

Gly Pro Asp Val Phe Ser Gly Ser Ser Tyr Pro Gly Val Gln Ser Leu
145 150 155 160

Leu Cys Ile Thr Pro Leu Ser Ile Ile Val Leu Cys Tyr Leu Gln Val
165 170 175

Trp Thr Ala Ile Arg Ala Val Ala Lys Gln Gln Lys Glu Ser Glu Ser
180 185 190

Thr Gln Lys Ala Glu Lys Glu Val Thr Arg Met Trp Val Met Val Leu
195 200 205

Ala Phe Cys Phe Cys Trp Gly Pro Tyr Ala Phe Phe Ala Cys Phe Ala

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                210                 215                 220

Ala Ala Asn Pro Gly Tyr Pro Phe His Pro Leu Met Ala Ala Leu Pro
225                 230                 235                 240

Ala Phe Phe Ala Lys Ser Ala Thr Ile Tyr Asn Pro Val Ile Tyr Val
                    245                 250                 255

Phe Met Asn Arg Gln Phe Arg Asn Cys Ile Leu Gln Leu Phe Gly Lys
            260                 265                 270

Lys Val Asp Asp Gly Ser Glu Leu Ser Ser Ala Ser Lys Thr Glu Val
        275                 280                 285

Ser Ser Val Ser Ser Val Ser Pro Ala
    290                 295
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(2) INFORMATION FOR SEQ ID NO:58:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 297 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:58:

```
Arg Cys Phe Val Val Thr Ala Ser Val Phe Thr Asn Gly Leu Val Leu
1               5                   10                  15

Ala Ala Thr Met Lys Phe Lys Lys Leu Arg His Pro Leu Asn Trp Ile
            20                  25                  30

Leu Val Asn Ile Ala Val Ala Asp Ile Ala Gly Thr Val Ile Ala Ser
        35                  40                  45

Thr Ile Ser Ile Val Asn Gln Val Ser Gly Tyr Phe Val Leu Gly His
    50                  55                  60

Pro Met Cys Val Leu Glu Gly Tyr Thr Val Ser Leu Cys Gly Ile Thr
65                  70                  75                  80

Gly Leu Trp Ser Leu Ala Ile Ile Ser Trp Glu Arg Trp Leu Trp Cys
                85                  90                  95

Lys Pro Phe Gly Asn Val Arg Phe Asp Ala Lys Ile Ala Ile Val Gly
            100                 105                 110

Ile Ala Phe Ser Trp Ile Trp Ser Ala Val Trp Thr Ala Pro Pro Ile
        115                 120                 125

Phe Gly Trp Ser Arg Tyr Trp Pro His Gly Leu Lys Thr Ser Cys Gly
    130                 135                 140

Pro Asp Val Phe Ser Gly Ser Ser Tyr Pro Gly Val Gln Ser Leu Val
145                 150                 155                 160

Ile Met Val Thr Cys Cys Ile Ile Pro Ile Ala Ile Ile Leu Cys Tyr
                165                 170                 175

Leu Gln Val Trp Leu Ala Ile Arg Ala Val Ala Lys Gln Gln Lys Glu
            180                 185                 190

Ser Glu Ser Thr Gln Lys Ala Glu Lys Glu Val Thr Arg Met Leu Phe
        195                 200                 205

Ala Tyr Cys Val Cys Trp Gly Pro Tyr Thr Phe Phe Ala Cys Phe Ala
    210                 215                 220
```

Ala Ala Asn Pro Gly Tyr Ala Phe His Pro Leu Met Ala Ala Leu Pro
225 230 235 240

Ala Tyr Phe Ala Lys Ser Ala Thr Ile Tyr Asn Pro Val Ile Tyr Val
245 250 255

Phe Met Asn Arg Gln Phe Arg Asn Cys Ile Leu Gln Leu Phe Gly Lys
260 265 270

Lys Val Asp Asp Gly Ser Glu Leu Ser Ser Ala Ser Lys Thr Glu Val
275 280 285

Ser Ser Val Ser Ser Val Ser Pro Ala
290 295

(2) INFORMATION FOR SEQ ID NO:59:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 305 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:59:
Gln Ala Ala Phe Met Gly Thr Val Phe Leu Ile Gly Phe Pro Leu Leu
1 5 10 15

Val Ala Thr Leu Ala Tyr Lys Lys Leu Arg Gln Pro Asn Tyr Ile Leu
20 25 30

Val Asn Val Ser Phe Gly Gly Phe Leu Leu Cys Ile Phe Ser Val Phe
35 40 45

Pro Val Phe Val Ala Ser Cys Asn Gly Tyr Phe Val Phe Gly Arg His
50 55 60

Val Cys Ala Leu Glu Gly Phe Leu Gly Thr Val Ala Gly Leu Val Thr
65 70 75 80

Gly Trp Ser Leu Ala Phe Leu Ala Phe Glu Arg Tyr Ile Val Ile Cys
85 90 95

Lys Pro Phe Gly Asn Phe Arg Phe Ser Ser Lys His Ala Leu Thr Val
100 105 110

Val Ile Ala Thr Trp Thr Ile Gly Ile Gly Val Ser Ile Pro Pro Phe
115 120 125

Phe Gly Trp Ser Arg Phe Ile Pro Glu Gly Leu Gln Cys Ser Cys Gly
130 135 140

Pro Asp Lys Tyr Thr Val Gly Thr Lys Tyr Arg Ser Glu Ser Tyr Thr
145 150 155 160

Trp Phe Leu Phe Ile Phe Cys Phe Ile Val Pro Leu Ser Leu Ile Cys
165 170 175

Phe Ser Tyr Thr Gln Leu Leu Arg Ala Leu Lys Ala Val Ala Ala Gln
180 185 190

Gln Gln Glu Ser Ala Thr Thr Gln Lys Ala Glu Arg Glu Val Ser Arg
195 200 205

Met Val Val Val Met Val Gly Ser Phe Cys Val Cys Tyr Val Pro Tyr
210 215 220

Ala Ala Phe Ala Met Tyr Met Val Asn Asn Arg Asn His Gly Leu Asp

225 230 235 240

Leu Arg Leu Val Arg Ile Pro Ser Phe Phe S r Lys Ser Ala Cys Ile
245 250 255

Tyr Asn Pro Ile Ile Tyr Cys Phe Met Asn Lys Gln Phe Gln Ala Cys
260 265 270

Ile Met Met Val Cys Gly Lys Ala Met Met Glu Ser Asp Thr Cys Ser
275 280 285

Ser Gln Lys Thr Glu Val Ser Thr Val Ser Ser Thr Gln Val Gly Pro
290 295 300

Asn
305

(2) INFORMATION FOR SEQ ID NO:60:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 293 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:60:

Leu Ile Tyr Gly Leu Phe Leu Ser Met Tyr Leu Val Thr Val Ile Gly
1 5 10 15

Asn Ile Ser Ile Ile Val Ala Ile Ile Ser Asp Pro Cys Leu His Thr
20 25 30

Pro Met Tyr Phe Phe Leu Ser Asn Leu Ser Phe Val Asp Ile Cys Phe
35 40 45

Ile Ser Thr Thr Val Pro Val Asn Thr Gln Thr Gln Asn Asn Val Ile
50 55 60

Thr Tyr Ala Gly Cys Ile Thr Gln Ile Tyr Phe Phe Leu Leu Phe Val
65 70 75 80

Glu Leu Asp Asn Phe Leu Leu Thr Ile Met Ala Tyr Asp Arg Tyr Val
85 90 95

Ala Ile Cys His Pro Met His Tyr Thr Val Ile Met Asn Tyr Lys Leu
100 105 110

Cys Gly Phe Leu Val Leu Val Ser Trp Ile Val Ser Val Leu His Ala
115 120 125

Leu Phe Gln Ser Leu Ala Leu Pro Phe Cys Thr His Leu Glu Ile Pro
130 135 140

His Tyr Phe Cys Glu Pro Asn Gln Val Ile Gln Leu Thr Cys Ser Asp
145 150 155 160

Ala Phe Leu Asn Asp Leu Val Ile Tyr Phe Thr Leu Val Leu Leu Ala
165 170 175

Thr Val Pro Ile Ala Gly Ile Phe Tyr Ser Tyr Phe Ala Ile Ser Ser
180 185 19-

Val His Gly Lys Tyr Lys Ala Phe Ser Thr Cys Ala Ser His Leu Ser
195 200 205

Val Val Ser Leu Phe Tyr Cys Thr Gly Leu Gly Val Tyr Leu Ser Ser
210 215 220

Ala Ala Asn Asn Ser Leu Ser Ala Thr Ala Ser Val Met Tyr Thr Val
225 230 235 240

Val Thr Pro Met Val Asn Pro Phe Ile Tyr Ser Leu Arg Asn Lys Asp
245 250 255

Val Lys Ser Val Leu Lys Lys Thr Leu Cys Glu Glu Val Ile Arg Ser
260 265 270

Pro Pro Ser Leu Leu His Phe Phe Leu Val Leu Cys His Leu Pro Cys
275 280 285

Phe Ile Phe Cys Tyr
290

(2) INFORMATION FOR SEQ ID NO:61:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 284 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:61:
Leu Leu Phe Leu Leu Phe Leu Ile Met Tyr Leu Ala Thr Val Leu Gly
1 5 10 15

Asn Leu Leu Ile Ile Leu Ala Ile Gly Gly Asp Ser Arg Leu His Thr
20 25 30

Pro Met Tyr Phe Phe Leu Ser Asn Leu Ser Phe Val Asp Val Cys Phe
35 40 45

Ser Ser Thr Thr Val Pro Lys Val Leu Ala Asn His Ile Leu Gly Ser
50 55 60

Gln Ala Ile Ser Phe Ser Gly Cys Leu Thr Gln Leu Tyr Phe Leu Ala
65 70 75 80

Val Phe Gly Asn Met Asp Asn Phe Leu Leu Ala Val Met Ser Tyr Asp
85 90 95

Arg Tyr Val Ala Ile Cys His Pro Leu His Tyr Thr Thr Ile Arg Gln
100 105 110

Leu Cys Val Leu Leu Val Val Gly Ser Trp Val Val Ala Asn Met Asn
115 120 125

Cys Leu Leu His Ile Leu Ile Met Ala Arg Lys Ser Phe Cys Ala Asp
130 135 140

Leu Pro His Phe Phe Cys Asp Gly Thr Pro Leu Leu Lys Leu Ser Cys
145 150 155 160

Ser Asp Thr His Leu Asn Glu Leu Met Ile Leu Thr Glu Gly Ala Val
165 170 175

Val Met Val Thr Pro Phe Val Cys Ile Leu Ile Ser Tyr Ile His Ile
180 185 190

Thr Cys Ala Val Leu Arg Val Ser Ser Pro Arg Gly Gly Trp Lys Ser
195 200 205

Phe Ser Thr Cys Gly Ser His Ile Ala Val Val Cys Leu Phe Tyr Gly
210 215 220

Thr Val Ile Ala Val Tyr Phe Asn Pro Ser Ser Ser His Leu Ala Gly

225 230 235 240

Arg Asp Met Ala Ala Ala Val Met Tyr Ala Val Val Thr Pro Met Ile
245 250 255

Asn Pro Phe Ile Tyr Ser Leu Arg Asn Ser Asp Met Lys Ala Ala Leu
260 265 270

Arg Lys Val Leu Ala Met Arg Phe Pro Ser Lys Gln
275 280

(2) INFORMATION FOR SEQ ID NO:62:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 277 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:62:

Leu Leu Phe Leu Leu Phe Leu Val Met Tyr Leu Leu Thr Val Val Gly
1 5 10 15

Asn Leu Ala Ile Ile Ser Leu Val Gly Ala His Arg Cys Leu Gln Pro
20 25 30

His Thr Pro Met Tyr Phe Phe Leu Cys Asn Leu Ser Phe Leu Glu Ile
35 40 45

Trp Phe Thr Thr Ala Cys Val Pro Lys Thr Leu Ala Thr Phe Ala Pro
50 55 60

Arg Gly Gly Val Ile Ser Leu Ala Gly Cys Ala Thr Lys Tyr Phe Val
65 70 75 80

Phe Ser Leu Gly Cys Thr Glu Tyr Phe Leu Leu Ala Val Met Ala Tyr
85 90 95

Asp Arg Tyr Leu Ala Ile Cys Leu Pro Leu Arg Tyr Gly Gly Ile Met
100 105 110

Arg Pro Gly Ile Ala Met Arg Leu Ala Leu Gly Ser Trp Leu Cys Gly
115 120 125

Phe Ser Ala Ile Thr Val Pro Ala Thr Leu Ile Ala Arg Leu Ser Phe
130 135 140

Cys Gly Ser Arg Val Ile Asn His Phe Phe Cys Asp Ile Ser Pro Trp
145 150 155 160

Ile Val Leu Ser Cys Thr Asp Thr Gln Val Val Glu Leu Val Ser Phe
165 170 175

Gly Ile Ala Phe Cys Val Ile Leu Gly Ser Cys Gly Ile Thr Leu Val
180 185 190

Ser Tyr Ala Lys Ile Pro Ser Ala Arg Gly Arg His Arg Ala Phe Ser
195 200 205

Thr Cys Ser Ser His Leu Thr Val Val Leu Ile Trp Tyr Gly Ser Thr
210 215 220

Ile Phe Leu His Val Arg Thr Ser Val Glu Ser Ser Leu Asp Leu Thr
225 230 235 240

Lys Ala Ile Thr Val Leu Asn Thr Ile Val Thr Pro Val Leu Asn Pro

245 250 255

Phe Ile Tyr Thr Leu Arg Asn Lys Asp Val Lys Glu Ala Leu Arg Arg
260 265 270

Thr Val Lys Gly Lys
275

(2) INFORMATION FOR SEQ ID NO:63:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 273 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:63:
Leu Ile Phe Ala Leu Phe Leu Ser Met Tyr Leu Val Thr Val Leu Gly
1 5 10 15

Asn Leu Leu Ile Ile Met Ala Ile Ile Thr Gln Ser His Leu His Thr
20 25 30

Pro Met Tyr Phe Phe Leu Ser Phe Val Asp Ile Cys Phe Thr Ser Thr
35 40 45

Thr Ile Pro Leu Val Asn Ile Tyr Thr Gln Ser Lys Ser Ile Thr Tyr
50 55 60

Glu Asp Cys Ile Ser Leu Val Phe Ala Glu Leu Gly Asn Phe Leu Leu
65 70 75 80

Ala Val Met Ala Tyr Asp Arg Tyr Val Ala Xaa Cys His Pro Leu Cys
85 90 95

Tyr Thr Val Ile Val Asn His Arg Leu Cys Ile Leu Leu Leu Leu Leu
100 105 110

Ser Trp Val Ile Ser Ile Phe Arg Ala Phe Ile Gln Ser Leu Ile Val
115 120 125

Leu Gln Leu Thr Phe Cys Gly Asp Val Lys Ile Pro His Phe Phe Cys
130 135 140

Glu Leu Asn Gln Leu Ser Gln Leu Thr Cys Ser Asp Asn Phe Pro Ser
145 150 155 160

His Leu Ile Met Asn Leu Val Pro Val Met Leu Ala Ala Ile Ser Phe
165 170 175

Ser Gly Ile Leu Tyr Ser Tyr Phe Ser Ile Ser Thr Val Gln Gly Lys
180 185 190

Tyr Lys Ala Phe Ser Thr Cys Ala Ser His Leu Ser Ile Val Ser Leu
195 200 205

Phe Tyr Ser Thr Gly Leu Gly Val Tyr Val Ser Ser Ala Val Val Gln
210 215 220

Ser Ser His Ser Ala Ala Ser Ala Ser Val Met Tyr Thr Val Val Pro
225 230 235 240

Met Leu Asn Pro Phe Ile Tyr Ser Leu Arg Asn Lys Asp Val Lys Arg
245 250 255

Ala Leu Glu Arg Leu Leu Glu Gly Asn Cys Lys Val His His Trp Thr
260 265 270

Gly

(2) INFORMATION FOR SEQ ID NO:64:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 269 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:64:

```
Leu Phe Tyr Ala Leu Phe Leu Val Met Tyr Leu Thr Thr Ile Leu Gly
1               5                  10                  15

Asn Leu Leu Ile Ile Val Leu Val Gln Leu Asp Ser Gln Leu His Thr
            20                  25                  30

Pro Met Tyr Leu Phe Leu Ser Asn Leu Ser Phe Ser Asp Leu Cys Phe
        35                  40                  45

Ser Ser Leu Lys Leu Leu Gln Asn Met Arg Ser Gln Asp Thr Ser Ile
    50                  55                  60

Pro Tyr Gly Gly Cys Leu Ala Gln Thr Tyr Phe Phe Met Val Phe Gly
65                  70                  75                  80

Asp Leu Ser Phe Leu Leu Val Ala Met Ala Tyr Asp Arg Tyr Val Ala
                85                  90                  95

Ile Cys Phe Leu Pro His Tyr Thr Ser Ile Met Ser Pro Lys Leu Cys
            100                 105                 110

Thr Cys Leu Val Leu Leu Leu Trp Met Leu Thr Thr Ser His Met Met
        115                 120                 125

Thr Leu Leu Ala Ala Arg Leu Ser Phe Cys Glu Asn Asn Trp Leu Asn
    130                 135                 140

Phe Phe Cys Asp Leu Phe Val Leu Leu Lys Ile Ala Cys Ser Asp Thr
145                 150                 155                 160

Tyr Ile Asn Glu Leu Phe Ile Met Ser Thr Leu Leu Ile Ile Ile Pro
                165                 170                 175

Phe Phe Leu Ile Val Met Ser Tyr Ala Lys Val Pro Ser Thr Gln Gly
            180                 185                 190

Ile Cys Lys Val Phe Ser Thr Cys Gly Ser His Leu Ser Val Val Ser
        195                 200                 205

Leu Phe Tyr Gly Thr Ile Ile Gly Leu Tyr Leu Cys Pro Ala Gly Asn
    210                 215                 220

Asn Ser Thr Val Lys Glu Met Val Met Ala Met Met Tyr Thr Val Val
225                 230                 235                 240

Thr Pro Met Ile Asn Pro Phe Ile Tyr Ser Leu Arg Asn Arg Asp Leu
                245                 250                 255

Arg Ala Leu Ile Arg Val Ile Cys Ser Met Ile Thr Leu
            260                 265
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(2) INFORMATION FOR SEQ ID NO:65:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 286 amino acids
(B) TYPE: amino acid

(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:65:

Leu Leu Phe Phe Leu Ser Leu Leu Xaa Tyr Val Leu Val Leu Thr Glu
1 5 10 15
Asn Met Leu Ile Ile Ile Ala Ile Arg Asn His Pro Thr Leu His Lys
20 25 30

Pro Met Tyr Phe Phe Leu Phe Leu Glu Ile Trp Tyr Val Thr Val Thr
35 40 45

Ile Pro Lys Leu Met Gly Phe Ile Gly Ser Lys Glu Asn His Gly Gln
50 55 60

Leu Ile Ser Phe Phe Ala Cys Met Thr Gln Leu Tyr Phe Phe Leu Gly
65 70 75 80

Leu Gly Cys Thr Glu Cys Val Leu Leu Ala Val Met Ala Tyr Asp Arg
85 90 95

Tyr Val Ala Ile Cys His Pro Leu His Tyr Pro Val Ile Val Ser Ser
100 105 110

Arg Ile Glx Val Leu Gly Ser Trp Ala Gly Gly Phe Gly Ile Ser Met
115 120 125

Val Lys Val Phe Leu Ile Ser Arg Leu Ser Tyr Cys Gly Pro Asn Thr
130 135 140

Ile Asn His Phe Phe Cys Asp Val Ser Pro Leu Leu Asn Leu Ser Cys
145 150 155 160

Thr Asp Met Ser Thr Ala Glu Leu Thr Asp Phe Val Ile Ala Ile Phe
165 170 175

Ile Leu Leu Gly Pro Leu Ser Val Thr Gly Ala Ser Tyr Met Arg Ile
180 185 190

Pro Ser Ala Ala Gly Arg His Lys Ala Phe Ser Thr Cys Ala Ser His
195 200 205

Leu Thr Val Val Ile Ile Phe Tyr Ala Ala Ser Ile Phe Ile Tyr Ala
210 215 220

Arg Pro Lys Ala Leu Ser Ala Phe Thr Asp Asn Lys Leu Val Ser Val
225 230 235 240

Leu Tyr Ala Val Ile Val Pro Leu Phe Asn Pro Ile Ile Tyr Cys Leu
245 250 255

Arg Asn Gln Asp Val Lys Arg Ala Leu Arg Arg Thr Leu His Leu Ala
260 265 270

Gln Asp Gln Glu Ala Asn Thr Asn Lys Gly Ser Lys Ile Gly
275 280 285

(2) INFORMATION FOR SEQ ID NO:66:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 275 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:66:

Leu Phe Phe Ala Leu Phe Leu Ile Met Tyr Leu Thr Thr Phe Leu Gly
1 5 10 15

Asn Leu Leu Ile Val Val Leu Val Gln Leu Asp Ser His Leu His Thr
20 25 30

Pro Met Tyr Leu Phe Leu Ser Asn Leu Ser Phe Ser Asp Leu Cys Phe
35 40 45

Ser Ser Val Thr Met Leu Lys Leu Leu Gln Asn Ile Gln Ser Gln Val
50 55 60

Pro Ser Ile Ser Tyr Ala Gly Cys Leu Trp Ile Phe Phe Phe Leu Leu
65 70 75 80

Phe Gly Tyr Leu Gly Asn Phe Leu Leu Val Ala Met Ala Tyr Asp Arg
85 90 95

Tyr Val Ala Ile Cys Phe Pro Leu His Tyr Thr Asn Ile Met Ser His
100 105 110

Lys Leu Cys Thr Cys Leu Leu Leu Val Phe Trp Ile Met Arg Ser Ser
115 120 125

His Ala Met Met Ile Thr Leu Ile Ala Ala Arg Leu Ser Phe Cys Glu
130 135 140

Asn Asn Val Leu Leu Asn Phe Phe Cys Asp Leu Phe Val Leu Leu Lys
145 150 155 160

Leu Ala Cys Ser Asp Thr Tyr Val Asn Glu Leu Met Ile His Ile Met
165 170 175

Glu Val Ile Ile Ile Val Ile Pro Phe Val Leu Ile Val Ile Ser Tyr
180 185 190

Ala Lys Val Pro Ser Thr Gln Ser Ile His Lys Val Phe Ser Thr Cys
195 200 205

Gly Ser His Leu Ser Val Val Ser Leu Phe Tyr Gly Thr Ile Ile Gly
210 215 220

Leu Tyr Leu Cys Pro Ser Gly Asp Asn Phe Ser Leu Lys Gly Ser Leu
225 230 235 240

Thr Val Val Thr Pro Ile Met Pro Phe Ile Tyr Ser Leu Arg Asn Arg
245 250 255

Asp Met Lys Gln Ala Leu Ile Arg Val Thr Cys Ser Lys Lys Ile Ser
260 265 270

Leu Pro Trp
275

(2) INFORMATION FOR SEQ ID NO:67:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 284 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:67:

Leu Phe Tyr Ala Leu Phe Leu Ala Met Tyr Leu Thr Thr Leu Leu Gly
1 5 10 15

Asn Leu Ile Ile Ile Ile Leu Ile Leu Leu Asp Ser His Leu His Thr
20 25 30

Pro Met Tyr Leu Phe Leu Ser Asn Leu Ser Phe Ala Asp Leu Cys Phe
35 40 45

Ser Ser Leu Lys Leu Leu Gln Asn Met Gln Ser Gln Val Pro Ser Ile
50 55 60

Pro Tyr Ala Gly Cys Leu Ala Gln Ile Tyr Phe Phe Leu Phe Phe Gly
65 70 75 80

Asp Leu Gly Asn Phe Leu Leu Val Ala Met Ala Tyr Asp Arg Tyr Val
85 90 95

Ala Ile Cys Phe Pro Leu His Tyr Met Ser Ile Met Ser Pro Lys Ile
100 105 110

Glx Val Ser Leu Val Val Leu Ser Trp Val Leu Thr Thr Phe His Ala
115 120 125

Met Leu His Thr Leu Ile Met Ala Arg Leu Ser Phe Cys Glu Asp Ser
130 135 140

Val Ile Pro His Tyr Phe Cys Asp Met Ser Thr Leu Leu Lys Val Ala
145 150 155 160

Cys Ser Asp Thr His Asp Asn Glu Leu Ala Ile Phe Ile Leu Gly Gly
165 170 175

Pro Ile Val Val Leu Pro Phe Leu Leu Ile Ile Val Ser Tyr Ala Arg
180 185 190

Ile Val Ser Ser Ile Phe Lys Val Pro Ser Ser Gln Ser Ile His Lys
195 200 205

Ala Phe Ser Thr Cys Gly Ser His Leu Ser Val Val Ser Leu Phe Tyr
210 215 220

Gly Thr Val Ile Gly Leu Tyr Leu Cys Pro Ser Ala Asn Asn Ser Glu
225 230 235 240

Val Lys Glu Thr Val Met Ser Ile Tyr Thr Met Val Pro Met Leu Asn
245 250 255

Pro Phe Ile Tyr Ser Leu Arg Asn Arg Asp Ile Lys Asp Ala Leu Glu
260 265 270

Lys Ile Met Cys Lys Lys Gln Ile Pro Ser Phe Leu
275 280

(2) INFORMATION FOR SEQ ID NO:68:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 277 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:68:
Leu Phe Tyr Ala Leu Phe Leu Ala Met Tyr Leu Thr Ile Ile Leu Gly
1 5 10 15

Asn Leu Leu Ile Ile Val Leu Val Arg Leu Asp Ser His Leu His Met
20 25 30

Tyr Leu Phe Leu Ser Asn Leu Ser Phe Ser Asp Leu Cys Phe Ser Ser
35 40 45

Val Thr Trp Lys Leu Leu Gln Asn Met Gln Ser Gln Val Pro Ser Ile
50 55 60

Ser Tyr Thr Gly Cys Leu Thr Gln Leu Tyr Phe Phe Met Val Phe Gly
65 70 75 80

Asp Trp Ser Phe Leu Leu Val Val Met Ala Tyr Asp Arg Tyr Val Ala
85 90 95

Ile Cys Phe Pro Leu Arg Tyr Thr Thr Ile Met Ser Thr Lys Phe Cys
100 105 110

Ala Ser Leu Val Leu Leu Leu Trp Met Leu Thr Met Arg His Ala Leu
115 120 125

Leu His Thr Leu Leu Ile Ala Arg Leu Ser Phe Cys Glu Asp Ser Val
130 135 140

Ile Leu His Phe Phe Cys Asp Ile Ser Ala Leu Leu Lys Leu Ser Cys
145 150 155 160

Ser Asp Ile Tyr Val Asn Glu Leu Met Ile Tyr Ile Leu Gly Gly Leu
165 170 175

Ile Ile Ile Ile Pro Phe Leu Leu Ile Val Met Ser Tyr Val Arg Ile
180 185 190

Phe Phe Ser Ile Leu Lys Phe Pro Ser Ile Gln Asp Ile Tyr Lys Val
195 200 205

Phe Ser Thr Cys Gly Ser His Leu Ser Val Val Thr Leu Phe Tyr Gly
210 215 220

Thr Ile Phe Gly Ile Tyr Leu Cys Pro Ser Gly Asn Asn Ser Thr Val
225 230 235 240

Lys Glu Ile Leu Thr Val Val Thr Pro Met Ile Asn Pro Phe Ile Tyr
245 250 255

Ser Leu Arg Asn Arg Asp Trp Arg Ala Leu Ile Arg Val Ile Cys Thr
260 265 270

Lys Lys Ile Ser Leu
275

(2) INFORMATION FOR SEQ ID NO:69:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 274 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:69:
Val Phe Tyr Ala Leu Phe Leu Ser Met Tyr Leu Thr Ile Val Leu Gly
1 5 10 15

Asn Leu Ile Ile Ile Ile Leu Ile His Leu Asp Ser His Leu His Thr
20 25 30

Pro Met Tyr Leu Phe Leu Ser Asn Leu Ser Phe Ser Asp Leu Cys Phe
35 40 45

Ser Ser Leu Lys Leu Leu Gln Asn Met Gln Ser Gln Val Pro Ser Ile
50 55 60

Pro Phe Ala Gly Cys Leu Thr Gln Leu Tyr Phe Tyr Leu Tyr Phe Ala
65 70 75 80

Asp Leu Glu Ser Phe Leu Leu Val Ala Met Ala Tyr Asp Arg Tyr Val
85 90 95

Ala Ile Cys Phe Pro Leu His Tyr Met Ser Ile Met Ser Pro Lys Leu
100 105 110

Cys Val Ser Leu Trp Leu Ser Trp Val Leu Thr Thr Phe His Ala Met
115 120 125

Leu His Thr Leu Ile Met Ala Arg Leu Ser Phe Cys Ala Asp Leu Pro
130 135 140

His Phe Phe Cys Asp Ile Ser Pro Leu Leu Lys Leu Ser Cys Ser Asp
145 150 155 160

Thr His Val Asn Glu Leu Val Ile Phe Leu Gly Leu Val Ile Val Ile
165 170 175

Pro Phe Val Leu Ile Ile Val Ser Tyr Ala Arg Val Val Ala Ser Ile
180 185 190

Leu Lys Val Pro Ser Val Arg Gly Ile His Lys Ile Phe Ser Thr Cys
195 200 205

Gly Ser His Leu Ser Val Val Ser Leu Phe Tyr Gly Thr Ile Ile Gly
210 215 220

Leu Tyr Leu Cys Pro Ser Ala Asn Asn Ser Thr Val Lys Glu Thr Leu
225 230 235 240

Thr Val Val Thr Pro Leu Pro Phe Ile Tyr Ser Leu Arg Asn Arg Asp
245 250 255

Met Lys Glu Ala Leu Ile Arg Val Leu Cys Lys Lys Lys Ile Thr Phe
260 265 270

Cys Leu

(2) INFORMATION FOR SEQ ID NO:70:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 345 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:70:
Leu Ala Ile Ala Val Leu Ser Leu Thr Leu Leu Gly Thr Phe Thr Val
1 5 10 15

Leu Glu Asn Leu Leu Val Leu Cys Val Ile Leu His Ser Arg Ser Leu
20 25 30

Arg Cys Arg Pro Ser Tyr His Phe Ile Gly Ser Leu Ala Val Ala Asp
35 40 45

Leu Leu Gly Ser Val Ile Phe Val Tyr Ser Phe Val Asp Phe His Val
50 55 60

Phe His Arg Lys Asp Ser Pro Asn Val Phe Leu Phe Lys Leu Gly Gly
65 70 75 80

Val Thr Ala Ser Phe Thr Ala Ser Val Gly Ser Leu Phe Leu Thr Ala
85 90 95

Ile Asp Arg Tyr Ile Ser Ile His Pro Pro Ile Ala Tyr Lys Arg Ile
100 105 110

Val Arg Arg Pro Lys Ala Val Val Ala Phe Cys Leu Met Thr Ile Ala
115 120 125

Ile Val Ile Ala Val Leu Pro Leu Leu Gly Trp Asn Cys Lys Lys Leu
130 135 140

Gln Ser Val Cys Cys Asp Ile Phe Pro Leu Ile Asp Gly Thr Tyr Leu
145 150 155 160

Met Phe Trp Ile Gly Val Thr Ser Val Leu Leu Leu Phe Ile Val Tyr
165 170 175

Ala Tyr Met Tyr Ile Leu Trp Lys Ala His Ser His Ala Val Arg Ala
180 185 190

Gln Arg Gly Thr Gln Lys Ser Ile Ile Ile His Thr Ser Glu Asp Gly
195 200 205

Lys Val Gln Val Thr Arg Pro Asp Gln Ala Arg Met Asp Ile Arg Leu
210 215 220

Ala Lys Thr Leu Val Leu Ile Leu Val Val Leu Ile Ile Cys Trp Gly
225 230 235 240

Pro Leu Leu Ala Ile Met Val Tyr Asp Val Phe Gly Leu Leu Ile Lys
245 250 255

Thr Val Phe Ala Phe Cys Ser Leu Leu Ile Asn Ser Thr Val Asn Pro
260 265 270

Ile Ile Tyr Ala Leu Arg Ser Lys Asp Leu Arg His Ala Phe Arg Ser
275 280 285

Trp Pro Ser Cys Glu Gly Thr Ala Gln Pro Leu Asp Asn Ser Met Gly
290 295 300

Asp Ser Asp Cys Leu His Lys His Ala Asn Asn Thr Ala Ser Met His
305 310 315 320

Arg Ala Ala Glu Ser Cys Ile Lys Ser Thr Val Lys Leu Ala Leu Val
325 330 335

Ser Thr Asp Thr Ser Ala Glu Ala Leu
340 345

(2) INFORMATION FOR SEQ ID NO:71:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 349 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:71:

Lys Ala Leu Leu Ile Val Ala Tyr Ser Phe Thr Ile Val Phe Ser Leu
1 5 10 15

Phe Gly Asn Val Leu Val Cys His Tyr Ile Phe Lys Asn Gln Arg Lys
20 25 30

Ile Ser Ala Thr Ser Leu Phe Ile Val Asn Leu Ala Val Ala Asp Ile
35 40 45

Ile Glu Thr Leu Leu Asn Thr Pro Phe Thr Leu Val Arg Phe Val Asn
50 55 60

Ser Thr Trp Tyr Phe Gly Lys Gly Met Leu His Val Ser Arg Phe Ala
65 70 75 80

Gln Tyr Cys Ser Leu His Val Ser Ala Leu Ile Leu Thr Ala Ile Ala
85 90 95

Val Asp Arg His Gln Val Ile Met Pro Leu Lys Pro Arg Ile Ser Ile
100 105 110

Thr Lys Gly Val Ile Tyr Ile Ala Val Ile Trp Val Met Thr Phe Phe
115 120 125

Ser Leu Pro His Ala Ile Cys Gln Lys Leu Phe Thr Phe Lys Tyr Ser
130 135 140

Glu Asp Ile Val Arg Ser Leu Cys Leu Asp Pro Phe Pro Glu Pro Ala
145 150 155 160

Asp Leu Phe Trp Lys Tyr Leu Asp Ile Ala Thr Phe Ile Leu Leu Tyr
165 170 175

Leu Leu Pro Leu Phe Ile Ile Ser Val Ala Tyr Ala Arg Val Ala Lys
180 185 190

Lys Leu Trp Leu Cys Asn Thr Ile Gly Asp Val Thr Thr Glu Gln Tyr
195 200 205

Leu Ala Leu Arg Arg Lys Lys Lys Thr Thr Val Lys Met Leu Val Leu
210 215 220

Val Val Val Leu Phe Ala Leu Cys Trp Phe Pro Leu Asn Cys Tyr Val
225 230 235 240

Leu Leu Leu Ser Ser Lys Ala Ile His Thr Asn Asn Ala Leu Tyr Phe
245 250 255

Ala Phe His Trp Phe Ala Met Ser Ser Thr Cys Tyr Asn Pro Phe Ile
260 265 270

Tyr Cys Trp Leu Asn Glu Asn Phe Arg Val Glu Leu Lys Ala Leu Leu
275 280 285

Ser Met Gln Pro Pro Pro Lys Pro Glu Asp Arg Leu Pro Ser Pro Val
290 295 300

Pro Ser Phe Arg Val Ala Trp Thr Glu Lys Ser His Gly Arg Arg Ala
305 310 315 320

Pro Leu Pro Asn His His Leu Pro Ser Ser Gln Ile Gln Ser Gly Lys
325 330 335

Thr Asp Leu Ser Ser Val Glu Pro Val Val Ala Met Ser
340 345

(2) INFORMATION FOR SEQ ID NO:72:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 301 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:72:

Ile Phe Thr Ile Ala Leu Ala Tyr Gly Ala Val Ile Ile Leu Gly Val
1 5 10 15

Ser Gly Asn Leu Ala Leu Ile Ile Ile Ile Leu Lys Gln Lys Glu Leu
20 25 30

Ile Leu Ile Val Asn Leu Ser Phe Ser Asp Leu Leu Val Ala Val Trp
35 40 45

Leu Pro Phe Thr Phe Val Tyr Thr Leu Ile Cys His Trp Val Phe Gly
50 55 60

Glu Cys Cys Lys Leu Asn Pro Phe Val Gln Cys Val Ser Ile Thr Val
65 70 75 80

Ser Ile Phe Ser Leu Val Leu Ile Ala Val Glu Arg His Gl.. Leu Ile
85 90 95

Ile Asn Pro Arg Gly Trp Arg Pro Asn Asn Arg His Ala Tyr Ile Gly
100 105 110

Ile Thr Val Ile Trp Val Ile Ala Val Ala Ser Ser Leu Pro Phe Val
115 120 125

Ile Tyr Gln Ile Leu Thr Asp Glu Pro Phe Gln Asn Val Ser Leu Ala
130 135 140

Ala Phe Lys Asp Lys Tyr Val Cys Phe Asp Lys Phe Pro Ser Asp Ser
145 150 155 160

His Arg Leu Ser Tyr Thr Thr Leu Leu Leu Val Leu Gln Tyr Phe Gly
165 170 175

Pro Leu Cys Phe Ile Phe Ile Cys Tyr Phe Lys Ile Tyr Ile Arg Leu
180 185 190

Lys Arg Arg Asn Asn Met Met Lys Ile Arg Asp Ser Lys Tyr Arg Ser
195 200 205

Ser Glu Thr Lys Arg Ile Asn Val Met Leu Leu Ser Ile Val Val Ala
210 215 220

Phe Ala Val Cys Trp Leu Pro Leu Thr Ile Phe Asn Ile Va.. Phe Asp
225 230 235 240

Trp Asn His Gln Ile Ile Ala Thr Cys Asn His Asn Leu Leu Phe Leu
245 250 255

Leu Cys His Leu Thr Leu Ser Thr Cys Val Asn Pro Ile Phe Tyr Gly
260 265 270

Phe Leu Asn Lys Asn Phe Gln Arg Asp Leu Gln Phe Phe Phe Asn Phe
275 280 285

Cys Asp Phe Arg Ser Arg Asp Gly Arg Thr Thr Arg Leu
290 295 300

(2) INFORMATION FOR SEQ ID NO:73:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 334 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:73:

Leu Thr Ser Val Val Phe Ile Leu Ile Cys Cys Phe Ile Ile Leu Glu
1 5 10 15

Asn Ile Phe Val Leu Leu Thr Ile Trp Lys Thr Lys Lys Phe His Arg
20 25 30

Pro Met Tyr Tyr Phe Ile Gly Asn Ile Ala Leu Ser Asp Leu Ile Ala
35 40 45

Gly Val Ala Tyr Thr Ala Asn Leu Leu Leu Ser Gly Ala Thr Thr Tyr
50 55 60

Lys Leu Thr Pro Ala Gln Trp Phe Leu Arg Glu Gly Ser Met Phe Val
65 70 75 80

Ala Leu Ser Leu Ser Val Phe Ser Leu Leu Ala Ile Ala Ile Glu Arg
85 90 95

Tyr Ile Thr Met Leu Lys Met Leu His Asn Gly Ser Asn Asn Phe Arg
100 105 110

Leu Phe Leu Leu Ile Ser Ala Cys Trp Val Ile Ser Leu Ile Leu Gly
115 120 125

Gly Leu Pro Ile Met Gly Trp Asn Cys Ile Ser Ala Leu Ser Ser Cys
130 135 140

Ser Thr Val Leu Pro Leu Tyr His Lys His Tyr Ile Leu Phe Cys Thr
145 150 155 160

Leu Ile Val Phe Thr Leu Leu Leu Leu Ser Ile Val Ile Leu Tyr Cys
165 170 175

Arg Ile Tyr Ser Leu Val Arg Thr Arg Ser Arg Arg Leu Thr Phe Arg
180 185 190

Lys Asn Ile Ser Lys Ala Ser Arg Ser Ser Glu Asn Val Ala Leu Leu
195 200 205

Lys Thr Val Ile Ile Val Leu Ser Val Phe Ile Ala Cys Trp Ala Pro
210 215 220

Leu Phe Ile Leu Leu Leu Leu Asp Val Gly Cys Lys Val Lys Thr Cys
225 230 235 240

Asp Ile Leu Phe Arg Ala Glu Tyr Phe Leu Val Ile Ala Val Ile Asn
245 250 255

Ser Gly Thr Asn Pro Ile Ile Tyr Thr Leu Thr Asn Lys Glu Met Arg
260 265 270

Arg Ala Phe Ile Arg Ile Met Cys Cys Lys Cys Pro Ser Gly Asp Ser
275 280 285

Ala Gly Lys Phe Lys Arg Pro Ile Ile Ala Gly Met Glu Phe Ser Arg
290 295 300

Ser Lys Ser Asp Asn Ser Ser His Pro Gln Lys Asp Glu Gly Asp Asn
305 310 315 320

Pro Glu Thr Ile Met Ser Ser Gly Asn Val Asn Ser Ser Ser
325 330

(2) INFORMATION FOR SEQ ID NO:74:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 236 amino acids

(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:74:

Ile Thr Tyr Tyr Ile Leu Ile Gly Leu Cys Ala Val Val Gly Asn Ile
1 5 10 15

Leu Leu Val Ile Trp Val Val Lys Leu Asn Arg Thr Leu Arg Thr Thr
20 25 30

Thr Phe Tyr Phe Ile Val Ser Ile Ala Leu Ala Asp Ile Ala Val Leu
35 40 45

Val Ile Pro Leu Ala Ile Ala Ser Ala Trp Arg Ser Arg Cys Thr Ser
50 55 60

Asn Cys Leu Phe Met Ser Cys Val Leu Leu Val Phe Thr His Ala Ser
65 70 75 80

Ile Met Ser Leu Leu Ala Ile Ala Val Asp Arg Tyr Leu Arg Val Lys
85 90 95

Leu Thr Val Arg Tyr Arg Thr Val Thr Thr Gln Arg Arg Ile Trp Leu
100 105 110

Phe Leu Gly Leu Cys Trp Leu Val Ser Phe Leu Val Gly Leu Thr Pro
115 120 125

Trp Gly Trp Asn Arg Lys Val Thr Leu Glu Leu Ser Gln Asn Ser Ser
130 135 140

Thr Leu Arg Glu Phe Lys Thr Pro Lys Ser Leu Phe Leu Val Leu Phe
145 150 155 160

Leu Phe Ala Leu Cys Trp Leu Pro Leu Ser Ile Ile Asn Phe Val Ser
165 170 175

Tyr Phe Asn Val Lys Ile Pro Glu Thr Leu Leu Gly Ile Leu Leu Ser
180 185 190

His Ala Asn Ser Leu Pro Ile Val Tyr Ala Cys Lys Lys Lys Phe Lys
195 200 205

Glu Thr Tyr Phe Val Ile Leu Arg Ala Cys Arg Leu Cys Gln Thr Ser
210 215 220

Asp Ser Leu Asp Ser Asn Leu Glu Gln Thr Thr Glu
225 230 235

(2) INFORMATION FOR SEQ ID NO:75:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 322 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:75:

Ala Ile Leu Ile Ser Phe Ile Tyr Ser Trp Cys Leu Val Gly Leu Cys
1 5 10 15

Gly Asn Ser Met Val Ile Tyr Val Ile Leu Arg Tyr Ala Lys Met Lys
20 25 30

Thr Ala Thr Asn Ile Tyr Ile Leu Asn Ile Ala Ile Ala Asp Glu Leu

35 40 45

Leu Val Pro Phe Leu Val Thr Ser Thr Leu Leu Arg His Trp Pro Phe
50 55 60

Gly Ala Leu Leu Cys Arg Leu Val Leu Ser Val Asp Ala Val Asn Met
65 70 75 80

Phe Thr Ser Ile Tyr Cys Leu Thr Val Leu Ser Val Asp Arg Tyr Val
85 90 95

Ala Val Val His Pro Ile Lys Ala Ala Arg Tyr Arg Arg Pro Thr Val
100 105 110

Ala Lys Val Val Asn Leu Gly Val Trp Val Leu Ser Leu Leu Val Ile
115 120 125

Leu Pro Ile Trp Phe Ser Arg Thr Ala Ala Asn Ser Asp Gly Thr Val
130 135 140

Ala Cys Asn Met Ile Trp Glu Pro Ala Gln Phe Trp Leu Val Gly Phe
145 150 155 160

Val Leu Tyr Thr Phe Leu Met Phe Leu Leu Pro Val Gly Ala Ile Cys
165 170 175

Leu Cys Tyr Val Leu Ile Ile Ala Lys Met Arg Met Val Ala Leu Lys
180 185 190

Ala Gly Trp Gln Gln Arg Lys Arg Ser Glu Arg Lys Ile Thr Leu Val
195 200 205

Met Met Val Val Met Val Phe Val Ile Cys Trp Phe Tyr Val Val Gln
210 215 220

Leu Val Asn Val Phe Ala Glu Gln Asp Asp Ala Thr Val Ser Gln Leu
225 230 235 240

Ser Val Ile Leu Gly Tyr Ala Asn Ser Cys Ala Asn Pro Ile Leu Tyr
245 250 255

Gly Phe Leu Ser Asp Asn Phe Lys Arg Ser Phe Gln Arg Ile Leu Cys
260 265 270

Leu Ser Leu Asn Ala Ala Glu Glu Pro Val Asp Tyr Tyr Ala Thr Ala
275 280 285

Leu Lys Ser Arg Ala Tyr Ser Val Glu Asp Phe Gln Pro Glu Asn Leu
290 295 300

Glu Ser Gly Gly Val Phe Arg Asn Cys Thr Cys Ala Ser Arg Ile Ser
305 310 315 320

Thr Leu

(2) INFORMATION FOR SEQ ID NO:76:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 298 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:76:
Val Thr Asn Tyr Ile Phe Leu Leu Leu Cys Leu Cys Gly Leu Val Gly
1 5 10 15

Asn Gly Leu Val Leu Trp Phe Phe Gly Phe Ser Ile Lys Arg Thr Pro
20 25 30

Phe Ser Ile Tyr Ile Tyr Phe Leu His Ile Ala Ser Ala Asp Gly Ile
35 40 45

Tyr Leu Phe Ser Lys Ala Val Ile Ala Leu Leu Asn Met Gly Thr Phe
50 55 60

Leu Gly Ser Phe Pro Asp Tyr Val Arg Arg Val Ser Arg Ile Val Gly
65 70 75 80

Leu Thr Phe Phe Ala Gly Val Ser Leu Leu Pro Ala Ile Ser Ile Glu
85 90 95

Arg Cys Val Ser Val Ile Phe Pro Met Trp Tyr Trp Arg Arg Arg Pro
100 105 110

Lys Arg Leu Ser Ala Gly Val Cys Ala Leu Leu Trp Leu Leu Ser Phe
115 120 125

Leu Val Thr Ser Ile His Asn Tyr Phe Cys Leu Leu Gly His Glu Ala
130 135 140

Ser Gly Thr Ala Cys Leu Asn Met Asp Ile Ser Leu Leu Gly Ile Leu
145 150 155 160

Leu Phe Phe Leu Phe Cys Pro Ile Met Val Leu Pro Cys Ile Ala Leu
165 170 175

Leu His Val Glu Cys Arg Ala Arg Arg Arg Gln Arg Ser Ala Lys Leu
180 185 190

Asn His Val Val Leu Ala Ile Val Ser Val Phe Leu Val Ser Ser Ile
195 200 205

Tyr Leu Gly Ile Asp Trp Phe Leu Phe Trp Val Phe Gln Ile Pro Ala
210 215 220

Pro Phe Pro Glu Tyr Val Arg Asp Leu Cys Ile Cys Ile Asn Ser Ser
225 230 235 240

Ala Lys Pro Ile Val Tyr Phe Ile Ala Gly Arg Asp Lys Ser Gln Arg
245 250 255

Leu Trp Glu Pro Leu Arg Val Val Phe Gln Arg Ala Leu Arg Asp Gly
260 265 270

Ala Glu Pro Gly Asp Ala Ala Ser Ser Thr Pro Asn Thr Val Thr Met
275 280 285

Glu Met Gln Cys Pro Ser Gly Asn Ala Ser
290 295

(2) INFORMATION FOR SEQ ID NO:77:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 299 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:77:
Thr Thr Glu Ala Val Leu Asn Thr Phe Ile Ile Phe Val Gly Gly Pro
1 5 10 15

Ala Ile Val Leu Ile Thr Gln Leu Leu Thr Asn Arg Val Leu Gly Tyr

20 25 30

Ser Thr Pro Thr Ile Tyr Met Arg Asn Leu Tyr Ser Thr Asn Ph Leu
35 40 45

Thr Leu Thr Val Leu Pro Phe Ile Val Leu Ser Asn Gln Trp Leu Leu
50 55 60

Pro Ala Cys Tyr Val Ala Ser Cys Lys Phe Leu Ser Val Ile Tyr Tyr
65 70 75 80

Ser Ser Cys Thr Val Gly Phe Ala Thr Val Ala Leu Ile Ala Ala Asp
85 90 95

Arg Tyr Arg Val Leu His Lys Arg Thr Tyr Ala Arg Gln Ser Tyr Arg
100 105 110

Ser Leu Leu Leu Thr Trp Leu Ala Gly Leu Ile Phe Ser Val Pro Ala
115 120 125

Ala Val Tyr Thr Thr Val Val Met His His Asp Ala Asn Asp Thr Asn
130 135 140

Asn Thr Asn Gly His Ala Thr Cys Val Leu Tyr Phe Val Ala Glu Glu
145 150 155 160

Val His Thr Val Leu Leu Ser Trp Lys Val Leu Leu Thr Met Val Trp
165 170 175

Gly Ala Ala Pro Val Ile Leu Phe Tyr Ala Phe Phe Tyr Ser Thr Val
180 185 190

Gln Arg Thr Ser Gln Lys Gln Arg Ser Arg Thr Leu Thr Phe Val Ser
195 200 205

Val Leu Leu Ile Ser Phe Val Ala Leu Gln Thr Pro Tyr Val Ser Leu
210 215 220

Met Ile Phe Asn Ser Tyr Ala Thr Thr Ala Trp Pro Met Cys Glu His
225 230 235 240

Leu Thr Leu Arg Arg Thr Ile Gly Thr Leu Ala Arg Val Val Pro His
245 250 255

Leu His Cys Leu Ile Asn Pro Ile Leu Tyr Ala Leu Leu Cys His Asp
260 265 270

Phe Leu Gln Arg Met Arg Gln Cys Phe Arg Gly Gln Leu Ile Asp Arg
275 280 285

Ala Phe Leu Arg Ser Gln Gln Asn Gln Arg Ala
290 295

(2) INFORMATION FOR SEQ ID NO:78:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 283 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:78:
Leu Gly Val Trp Leu Met Ile Val Gly Thr Phe Leu Leu Val Ile Thr
1 5 10 15

Thr Ile Leu Tyr Tyr Arg Arg Lys Lys Lys Ser Pro Ser Asp Thr Tyr
20 25 30

Ile Cys Asn Leu Ala Val Ala Asp Leu Leu Ile Val Val Gly Leu Pro
35 40 45

Phe Phe Leu Glu Tyr Ala Lys His His Pro Lys Leu Ser Arg Glu Val
50 55 60

Val Cys Ser Gly Leu Asn Ala Cys Phe Tyr Ile Cys Leu Phe Ala Gly
65 70 75 80

Val Cys Phe Leu Ile Asn Leu Ser Met Asp Arg Tyr Cys Val Ile Val
85 90 95

Trp Gly Val Glu Leu Asn Arg Val Arg Asn Asn Lys Arg Ala Thr Cys
100 105 110

Trp Val Val Ile Phe Trp Ile Ile Ala Val Leu Met Gly Met Pro His
115 120 125

Tyr Ile Met Tyr Ser His Thr Asn Asn Glu Cys Val Gly Trp Phe Ala
130 135 140

Asn Glu Thr Ser Cys Trp Phe Pro Val Phe Leu Asn Thr Lys Val Asn
145 150 155 160

Ile Cys Gly Tyr Leu Ala Pro Ile Ala Leu Met Ala Tyr Tyr Asn Arg
165 170 175

Met Val Arg Phe Ile Ile Asn Tyr Val Gly Lys Trp Phe Met Gln Thr
180 185 190

Leu His Val Leu Leu Val Val Val Val Ser Phe Ala Ser Phe Trp Phe
195 200 205

Pro Phe Asn Leu Ala Leu Phe Leu Glu Ser Ile Arg Leu Ile Ala Gly
210 215 220

Val Tyr Asn Asp Thr Leu Gln Asn Val Ile Ile Phe Cys Leu Tyr Val
225 230 235 240

Gly Gln Phe Ile Ala Tyr Val Arg Ala Cys Leu Asn Pro Gly Ile Tyr
245 250 255

Ile Leu Val Cys Thr Trp Phe Leu Arg Val Phe Ala Cys Cys Cys Val
260 265 270

Lys Gln Glu Ile Pro Tyr Gln Asp Ile Asp Ile
275 280

(2) INFORMATION FOR SEQ ID NO:79:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 295 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:79:
Pro Val Thr Leu Phe Leu Tyr Gly Val Val Phe Leu Phe Gly Ser Ile
1 5 10 15

Gly Asn Phe Leu Val Ile Phe Thr Ile Thr Trp Arg Arg Arg Ile Gln
20 25 30

Cys Ser Gly Asp Val Tyr Phe Ile Asn Leu Ala Ala Ala Asp Leu Leu
35 40 45

Phe Val Cys Thr Leu Pro Leu Trp Met Gln Tyr Leu Leu Asn His Asn

50 55 60

Ser Leu Ala Ser Leu Ile Pro Cys Thr Leu Leu Thr Ala Cys Phe Tyr
65 70 75 80

Val Ala Ile Thr Ala Ser Leu Cys Phe Ile Thr Glu Ile Ala Leu Ile
85 90 95

Asp Arg Tyr Tyr Ala Ile Val Tyr Met Arg Tyr Arg Pro Val Lys Ile
100 105 110

Gln Ala Cys Leu Phe Ser Ile Phe Trp Trp Ile Phe Ala Val Ile Ile
115 120 125

Ala Ile Pro His Phe Met Val Val Ile Thr Lys Lys Asp Asn Gln Cys
130 135 140

Met Thr Asp Tyr Asp Tyr Leu Glu Val Ser Tyr Pro Ile Ile Leu Asn
145 150 155 160

Val Glu Leu Met Leu Gly Ala Phe Val Ile Pro Leu Ser Val Ile Ser
165 170 175

Tyr Cys Tyr Tyr Arg Ile Ser Arg Ile Val Ala Val Ser Gln Ser Arg
180 185 190

His Lys Gly Arg Ile Val Arg Val Leu Ile Ala Trp Leu Val Phe Ile
195 200 205

Ile Phe Trp Leu Pro Tyr His Leu Thr Leu Phe Val Asp Thr Ile Ile
210 215 220

Lys Leu Leu Lys Trp Ile Ser Ser Ser Cys Glu Phe Glu Arg Ser Leu
225 230 235 240

Lys Arg Ala Leu Ile Leu Thr Glu Ser Leu Ala Phe Cys His Cys Cys
245 250 255

Leu Asn Pro Leu Leu Tyr Val Phe Val Ile Gly Thr Lys Phe Arg Lys
260 265 270

Asn Tyr Thr Val Cys Trp Pro Ser Phe Ala Ser Asp Ser Phe Pro Ala
275 280 285

Met Tyr Pro Gly Thr Arg Ala
290 295

(2) INFORMATION FOR SEQ ID NO:80:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 31 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:80:
Asp Asp Asp Asp Asn Ile Trp Ser Ile Phe Asp Trp Ile Gly Tyr Leu
1 5 10 15

Asn Ser Ile Ser Met Val Ile Tyr Thr Leu Phe Lys Lys Lys Lys
20 25 30

(2) INFORMATION FOR SEQ ID NO:81:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 34 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single

(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:81:

Asp Asp Asp Asp Asn Ile Trp Asn Ile Phe Ser Thr Ile Gly Tyr Leu
1 5 10 15

Asn Ser Ile Ser Pro Val Ser Val Ile Met His Ile Tyr Gly Lys Lys
20 25 30

Lys Lys

(2) INFORMATION FOR SEQ ID NO:82:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 29 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:82:

Asp Asp Asp Asp Gly Tyr Ser Ile Tyr Asp Thr Leu Val Thr Phe Ala
1 5 10 15

Ile Asn Pro Val Tyr Ile Thr Val Phe Lys Lys Lys Lys
20 25

(2) INFORMATION FOR SEQ ID NO:83:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 31 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:83:

Asp Asp Asp Asp Asn Ala Trp Ser Ala Phe Asp Trp Ala Leu Tyr Leu
1 5 10 15

Asn Ser Ile Ser Met Ala Ile Tyr Thr Tyr Ala Lys Lys Lys Lys
20 25 30

(2) INFORMATION FOR SEQ ID NO:84:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 23 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:84:

Leu Phe Ser Phe Ile Thr Trp Leu Gly Tyr Ala Asn Ser Ser Leu Asn
1 5 10 15

Pro Ile Ile Tyr Thr Thr Phe
20

(2) INFORMATION FOR SEQ ID NO:85:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 23 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:85:

Tyr Thr Ile Tyr Ser Ser Ser Val Val Phe Phe Ala Pro Ser Leu Ala
1 5 10 15

Ile Met Val Ile Thr Tyr Thr
20

(2) INFORMATION FOR SEQ ID NO:86:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:86:
Ile Trp Leu Thr Ser Asp Ile Met Ser Thr Ser Ser Ile Leu His Asn
1 5 10 15

Leu Cys Val Ile Ser Phe
20

(2) INFORMATION FOR SEQ ID NO:87:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:87:
Ile Trp Ser Ile Phe Ser Ser Asp Ile Val Val Gly Tyr Ala Asn His
1 5 10 15

Ser Ser Leu Ala Ile Met Cys Pro Ile Val Ile Tyr Thr Va:
20 25 30

(2) INFORMATION FOR SEQ ID NO:88:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 29 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:88:
Ile Phe Thr Ile Phe Ser Ser Asp Ile Ala Val Gly Tyr Ala Asn His
1 5 10 15

Ser Ser Ala Ala Ile Met Pro Ile Val Ile Tyr Ser Val
20 25

(2) INFORMATION FOR SEQ ID NO:89:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 24 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:89:
Lys Asn Ala Ser Ala Leu Leu Ser Val Ile Ile Ile Asn Ser Ile Gly
1 5 10 15

Gly Asn Val Val Thr Ala Val Ser
20

(2) INFORMATION FOR SEQ ID NO:90:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:90:
Tyr Phe Leu Met Ser Leu Ala Val Thr Asp Leu Val Val Ser Phe Val
1 5 10 15

Met Pro Val Ser Ala Leu
20

(2) INFORMATION FOR SEQ ID NO:91:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 23 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:91:
Ala Ile Thr Lys Ile Ala Ile Thr Trp Ala Ile Ser Gly Val Ser Val
1 5 10 15

Pro Phe Ile Pro Val Trp Gly
20

(2) INFORMATION FOR SEQ ID NO:92:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 24 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:92:
Leu Gly Ile Ile Phe Gly Thr Phe Ile Ile Ile Trp Leu Pro Phe Phe
1 5 10 15

Ile Thr Asn Leu Val Ser Pro Ile
20

(2) INFORMATION FOR SEQ ID NO:93:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 23 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:93:
Ile Trp Ile Ser Leu Asp Val Leu Phe Ser Thr Ala Ser Ser Ile Met
1 5 10 15

His Leu Cys Ala Ile Ser Leu
20

(2) INFORMATION FOR SEQ ID NO:94:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 23 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:94:
Gly Tyr Thr Ile Tyr Ser Thr Leu Val Thr Phe Tyr Ile Pro Ser Val
1 5 10 15

Ile Met Val Ile Thr Tyr Gly
20

(2) INFORMATION FOR SEQ ID NO:95:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 23 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:95:

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Leu Leu Asn Phe Phe Asn Trp Ile Gly Tyr Leu Asn Ser Leu Ile Asn
1               5                  10                  15

Pro Val Ile Tyr Thr Leu Phe
            20
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WHAT IS CLAIMED IS:

1. A G-protein coupled receptor polypeptide, consisting essentially of an amino acid sequence of 15 to 40 amino acids substantially corresponding to a fragment or consensus peptide of a transmembrane domain of a G-protein coupled receptor, wherein said polypeptide has a GPR-related biological activity selected from binding a GPR ligand or modulating GPR ligand binding to a GPR.

2. A polypeptide according to claim 1, wherein said polypeptide is selected from a synthetic polypeptide, a recombinant polypeptide or a purified polypeptide.

3. A polypeptide according to claim 1, wherein said G-protein coupled receptor is a receptor selected from a cAMP receptor, an adenosine receptor, a β-adrenergic receptor, a muscarinic acetylcholine receptor, an α-adrenergic receptor, a serotonin receptor, a histamine H2 receptor, a thrombin receptor, a kinin receptor, a follicle stimulating hormone receptor, an opsin, a rhodopsin, an odorant receptor, a cytomegalovirus receptor, or a *mas* oncogene GPR.

4. A polypeptide according to claim 1, wherein said transmembrane domain is selected from at least one of transmembrane domain TM1, TM2, TM3, TM4, TM5, TM6 or TM7.

5. A polypeptide according to claim 3, wherein said transmembrane domain is a D_2 receptor transmembrane segment III or segment V.

6. A polypeptide according to claim 4, wherein said polypeptide has the amino acid sequence of Fig. 2 (SEQ ID NO:2).

7. A polypeptide according to claim 4, wherein said polypeptide has the amino acid sequence of Fig. 3 (SEQ ID NO:3).

8. A polypeptide according to claim 4, wherein said polypeptide has an amino acid sequence selected from one of SEQ ID NOS:80-95.

9. A polypeptide according to claim 4, wherein said polypeptide has an amino acid sequence of one of SEQ ID NOS:96-348.

10. A polypeptide according to claim 9, wherein said polypeptide has an amino acid sequence from one of SEQ ID NOS:96-225.

11. A polypeptide according to claim 9, wherein said polypeptide has an amino acid sequence from one of SEQ ID NOS:226-289.

12. A polypeptide according to claim 9, wherein said polypeptide has an amino acid sequence from one of SEQ ID NOS:290-297.

13. A polypeptide according to claim 9, wherein said polypeptide has an amino acid sequence from one of SEQ ID NOS:298-324.

14. A polypeptide according to claim 9, wherein said polypeptide has an amino acid sequence from one of SEQ ID NOS:325-338.

15. A polypeptide according to claim 9, wherein said polypeptide has an amino acid sequence from one of SEQ ID NOS:339-348.

16. A polypeptide according to claim 3, wherein said transmembrane domain is a dopamine receptor transmembrane domain selected from the group consisting of a D_1, D_2, D_3, D_4 or D_5 transmembrane domain.

17. A composition comprising a polypeptide according to claim 1, or a pharmaceutically acceptable ester, ether, sulfate, carbonate, glucuronide or salt thereof, and a pharmaceutically acceptable carrier.

18. A composition according to claim 16, wherein said transmembrane domain is D_2 receptor transmembrane segment III or segment V.

19. A composition according to claim 18, further comprising a drug selected from a phenothiazine derivative, a thioxanthine derivative, a butyrophenone derivative, a dihydroindolone, a dibenzoxazepine derivative and an atypical neuroleptic.

20. A method for treating a subject suffering from a pathology related to an abnormality of a G-protein coupled receptor, comprising administering to said subject a therapeutically effective amount of composition according to claim 16.

21. The method of claim 20, wherein said pathology is a psychotic disorder.

22. The method of claim 21, wherein said psychotic disorder is a schizophrenia.

23. The method of claim 20, wherein said composition is administered to provide said polypeptide, fragment or consensus peptide thereof, in an amount ranging from about 0.01 μg to 100 mg/kg per day.

24. The method of claim 23, wherein said composition is administered to provide said polypeptide, fragment or consensus peptide thereof, in an amount ranging from about 10μg to 10 mg/kg per day.

25. The method of claim 20, wherein said administering is by oral, mucosal, intravenous, intramuscular or parenteral administration.

26. A method for producing a polypeptide according to claim 1, wherein said polypeptide is a recombinant polypeptide obtained from a recombinant host which expresses a heterologous nucleic acid encoding said polypeptide, comprising the steps of:

(A) providing a host comprising a recombinant nucleic acid encoding a polypeptide according to claim 1 in expressible form;

(B) culturing said host under conditions such that said polypeptide is expressed in recoverable amounts; and

(C) recovering said polypeptide produced by said host.

27. The method of claim 26, further comprising:

(D) purifying said polypeptide.

28. The method of claim 26, wherein said host is a bacteria or a eukaryotic cell.

29. The method of claim 28, wherein said eukaryotic cell is a mammalian cell, an insect cell or a yeast cell.

30. A method for producing a polypeptide according to claim 1, comprising:

(A) chemically synthesizing a polypeptide according to claim 1 in recoverable amounts; and

(B) recovering said polypeptide.

31. A method for isolating a G-protein coupled receptor, fragment or consensus sequence thereof, or a protein that binds the G-protein coupled receptor, comprising

(A) providing a bound support, said support being bound to a polypeptide according to claim 1, or an antibody, anti-idiotype antibody, or a fragment thereof;

(B) contacting a sample containing said G-protein coupled receptor or said protein that binds a G-protein coupled receptor to said bound support, such that said receptor or protein is reversibly bound to said bound support; and

(C) recovering said receptor or protein that is attached to the bound support by dissociating the receptor or protein under conditions that cause elution or dissociation of the receptor or protein from said bound support.

32. A method according to claim 31, wherein said GPR is a dopamine receptor.

33. An antibody, anti-idiotype antibody or a fragment of said antibody or anti-idiotype antibody, that specifically displays an epitope of a G-protein coupled receptor polypeptide, according to claim 1.

34. A recombinant nucleic acid comprising a nucleotide sequence encoding a G-protein coupled receptor polypeptide according to claim 1.

35. A vector comprising a nucleic acid according to claim 34.

36. A host cell comprising the nucleic acid of claim 34.

37. A host cell according to claim 36, wherein said host cell is selected from a mammalian cell, a yeast cell, a bird cell or an insect cell.

38. A host cell according to claim 36, wherein, when said nucleic acid is expressed as said receptor polypeptide in said host cell, a receptor binding molecule comprising said *env* binding domain binds to said receptor polypeptide.

39. A host cell according to claim 37, wherein said host cell is a mammalian cell selected from a human cell, a primate cell or a rodent cell.

40. A method for isolating a protein that binds a G-protein coupled receptor, comprising

(A) providing a bound support, said support being bound to a polypeptide according to claim 1, or anti-idiotype antibody thereto;

(B) contacting a sample containing said protein that binds a G-protein coupled receptor to said bound support, such that said protein is reversibly bound to said bound support; and

(C) recovering said protein that is attached to the bound support by dissociating the receptor or protein under conditions that cause elution or dissociation of the protein from said bound support.

41. A method according to claim 40, wherein said GPR is a dopamine receptor.

FIGURE 1

DDIFVTLDVLFSTASILNLSAISLKKK

FIGURE 2

DYAIFVLYASAWLSFNCPFIVTLNIK

FIGURE 3

KAVVYSSIVSFYVFID

FIGURE 4

DCDVFVFVDIMLCTASIFNLCAISVGK

FIGURE 5

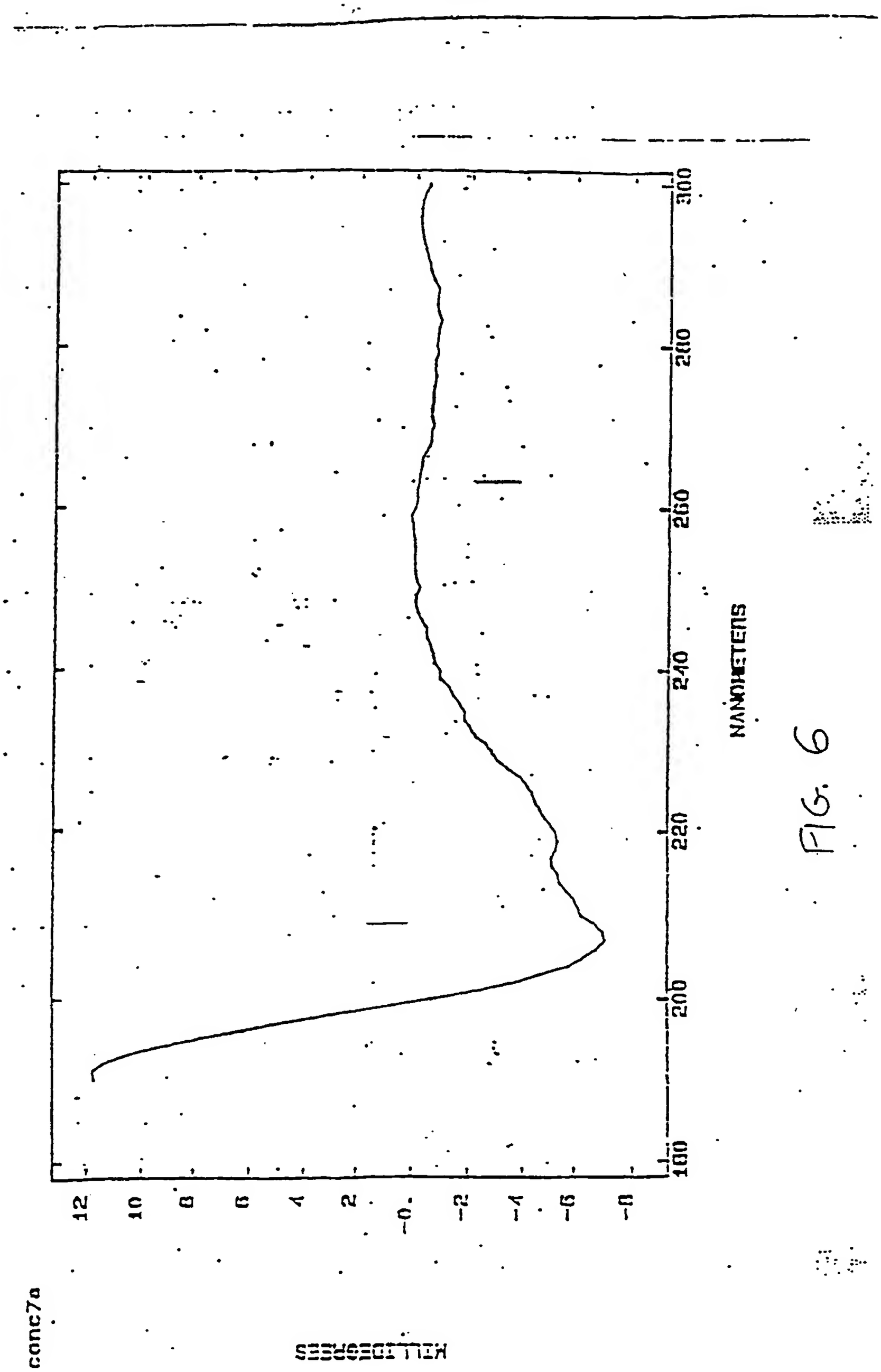
300
280
260
240
220
200
180
NANOMETERS
12
10
8
6
4
2
0
-2
-4
-6
-8
MILLIDEGREES
conc7a

FIG. 6

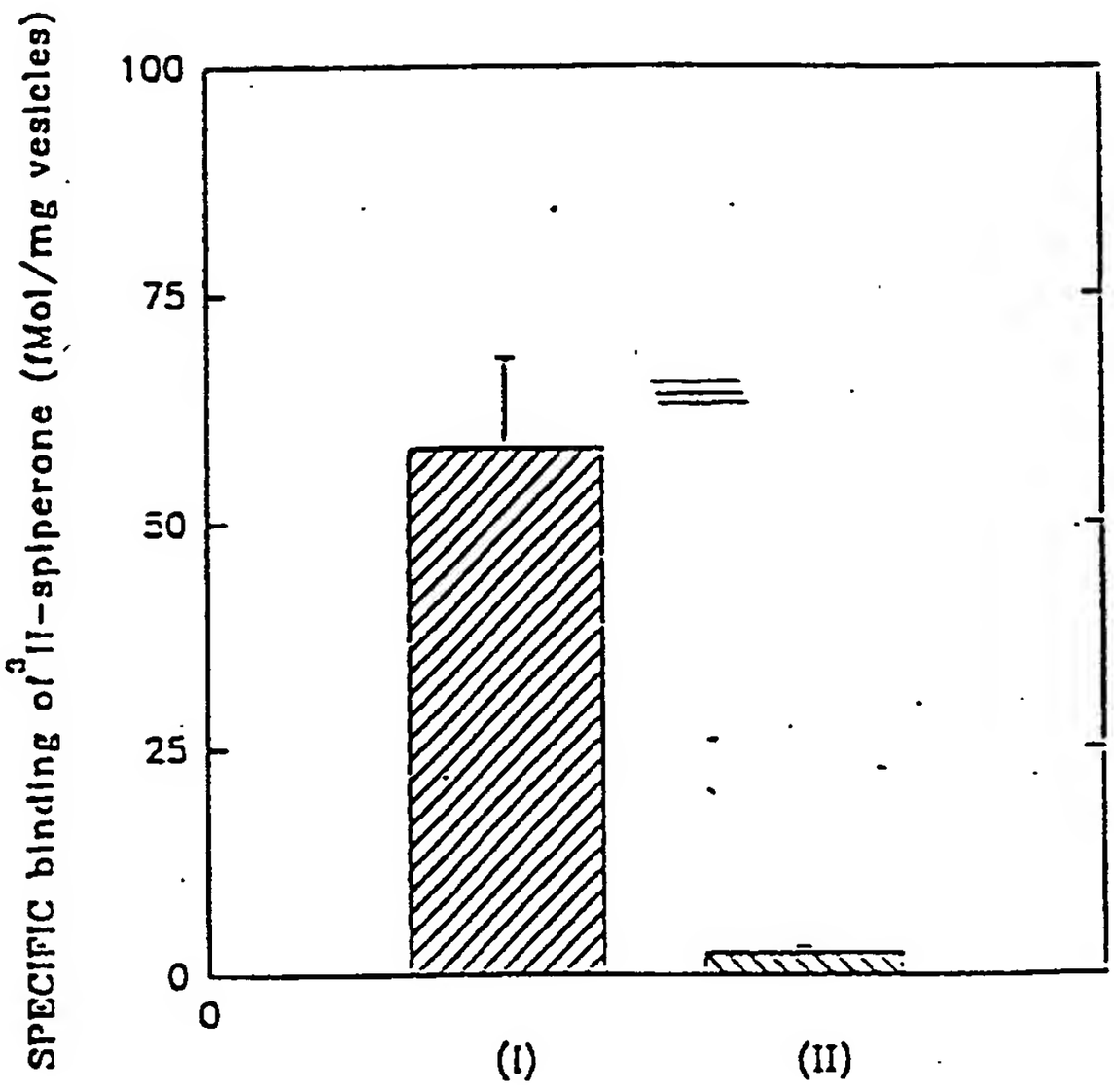
SPECIFIC binding of ^{3}H-spiperone (fMol/mg vesicles)
100
75
50
25
0
0
(I)
(II)

FIGURE 7

1. Dictyostelium cAMP receptor (Klein et al., 1988)
2. Dog adenosine A2 receptor (RDC3) (Libert et al., 1989b)
3. Dog adenosine A1 receptor (RDC7) (Libert et al., 1989b)

4. Human m1 muscarinic acetylcholine receptor (Peralta et al., 1987)
5. Human m2 muscarinic acetylcholine receptor (Peralta et al., 1987)
6. Human m3 muscarinic acetylcholine receptor (Peralta et al., 1987)
7. Human m4 muscarinic acetylcholine receptor (Peralta et al., 1987)
8. Human m5 muscarinic acetylcholine receptor (Bonner et al., 1988)

9. Human beta 1 adrenergic receptor (Frielle et al., 1987)
10. Human beta 2 adrenergic receptor (Kobilka et al., 1987a)
11. Human beta 3 adrenergic receptor (Emorine et al., 1989)
12. Cow alpha 1 adrenergic receptor (Schwinn et al., 1990)
13. Rat alpha 1B adrenergic receptor (Voigt, et al., 1990)
14. Human alpha 2 C4 adrenergic receptor (Regan et al., 1988)
15. Human alpha 2 C2 adrenergic receptor (Lomasney et al., 1990)
16. Human alpha 2 C10 adrenergic receptor (Kobilka et al., 1987c)
17. Rat alpha 2 adrenergic receptor R2D (Lanier et al., 1991)
18. Drosophila octopamine receptor (Arakawa et al., 1990)
19. Human dopamine D1 receptor (Dearry et al., 1990)
20. Human dopamine D5 receptor (Sunahara et al., 1991)
21. Human dopamine D2 receptor (Grandy et al., 1989)
22. Human dopamine D3 receptor (Giros et al., 1990)
23. Human dopamine D4 receptor (Van Tol et al., 1991)
24. Human serotonin 1d receptor (RDC4) (Hamblin and Metcalf, 1991)
25. Human serotonin 1a receptor (Kobilka et al., 1987b)
26. Rat serotonin 1c receptor (Julius et al., 1988)
27. Rat serotonin 2 receptor (Julius et al., 1990)
28. Human histamine H2 receptor (Gantz et al., 1991)

29. Human N-formyl peptide receptor (Boulay et al., 1990)
30. Human C5a anaphylatoxin receptor.(Gerard and Gerard, 1991)
31. Human thrombin receptor (Vu et al., 1991)
32. Human thromboxane A2 receptor (Hirata et al., 1991)
33. Human IL-8 receptor (Murphy and Tiffany, 1991)
34. Guinea-pig platelet-activating factor receptor (Honda et al, 1991)
35. Cow endothelin 1 receptor (Arai et al., 1990)
36. Rat non-isopeptide selective endothelin receptor (Sakurai et al., 1990)
37. Mouse bombesin/gastrin releasing peptide receptor (Spindel et al., 1991)
38. Rat neuromedin B preferring bombesin receptor (Wada et al., 1991)
39. Human vasoactive intestinal peptide (Sreedharan et al., 1991)
40. Rat neurotensin receptor (Tanaka et al., 1990)
41. Rat bradykinin receptor (McEachern et al., 1991)
42. Mouse thyrotropin-releasing hormone receptor (Straub et al., 1990)
43. Human neurokinin A (SK) receptor (Gerard et al., 1990)
44. Rat substance P receptor (Yokota et al., 1989)
45. Rat neuromedin K receptor (Shigemoto et al., 1990)
46. Bovine adrenal angiotensin II type-1 receptor (Sasaki et al. 1991)
47. Human mas oncogene (angiotensin) receptor (Young et al., 1986)

48. Human lutropin-choriogonadotropin receptor (Frazier et al., 1990)
49. Human thyrotropin receptor (Libert et al., 1989a)
50. Human follicle stimulating hormone receptor (Minegish et al., 1991)

51. Human rhodopsin (Nathans and Hogness, 1984)
52. Human green opsin (Nathans et al., 1986)
53. Human red opsin (Nathans et al., 1986)
54. Human blue opsin (Nathans et al., 1986)

55. Odorant receptor F3 (Buck and Axel, 1991)
56. Odorant receptor F5 (Buck and Axel, 1991)
57. Odorant receptor F6 (Buck and Axel, 1991)
58. Odorant receptor F12 (Buck and Axel, 1991)
59. Odorant receptor I3 (Buck and Axel, 1991)
60. Odorant receptor I7 (Buck and Axel, 1991)
61. Odorant receptor I8 (Buck and Axel, 1991)
62. Odorant receptor I9 (Buck and Axel, 1991)
63. Odorant receptor I14 (Buck and Axel, 1991)
64. Odorant receptor I15 (Buck and Axel, 1991)

65. Human cannabinoid receptor (Matsuda et al., 1990)
66. Mouse Glucocorticoid-induced receptor (Hartzican et al., 1991)
67. Rat FCSR (Eva et al., 1990)
68. Human endothelial cell G2R (Ala and Maciag, 1990)
69. Rat testis G-protein coupled receptor 1 (Meyerhof et al. 1991a)
70. Rat RCH2 (Meyerhof, DNA and Cell Biology, in press. 1991b).
71. Human thoracic aorta G2R (Ross et al., 1990)
72. Cytomegalovirus (Human) G2R, US33 (Chee et al., 1990)
73. Cytomegalovirus (Human) G2R, US27 (Chee et al., 1990)
74. Cytomegalovirus (Human) G2R, US28 (Chee et al., 1990)

FIGURE 8A

FIGURE 8B

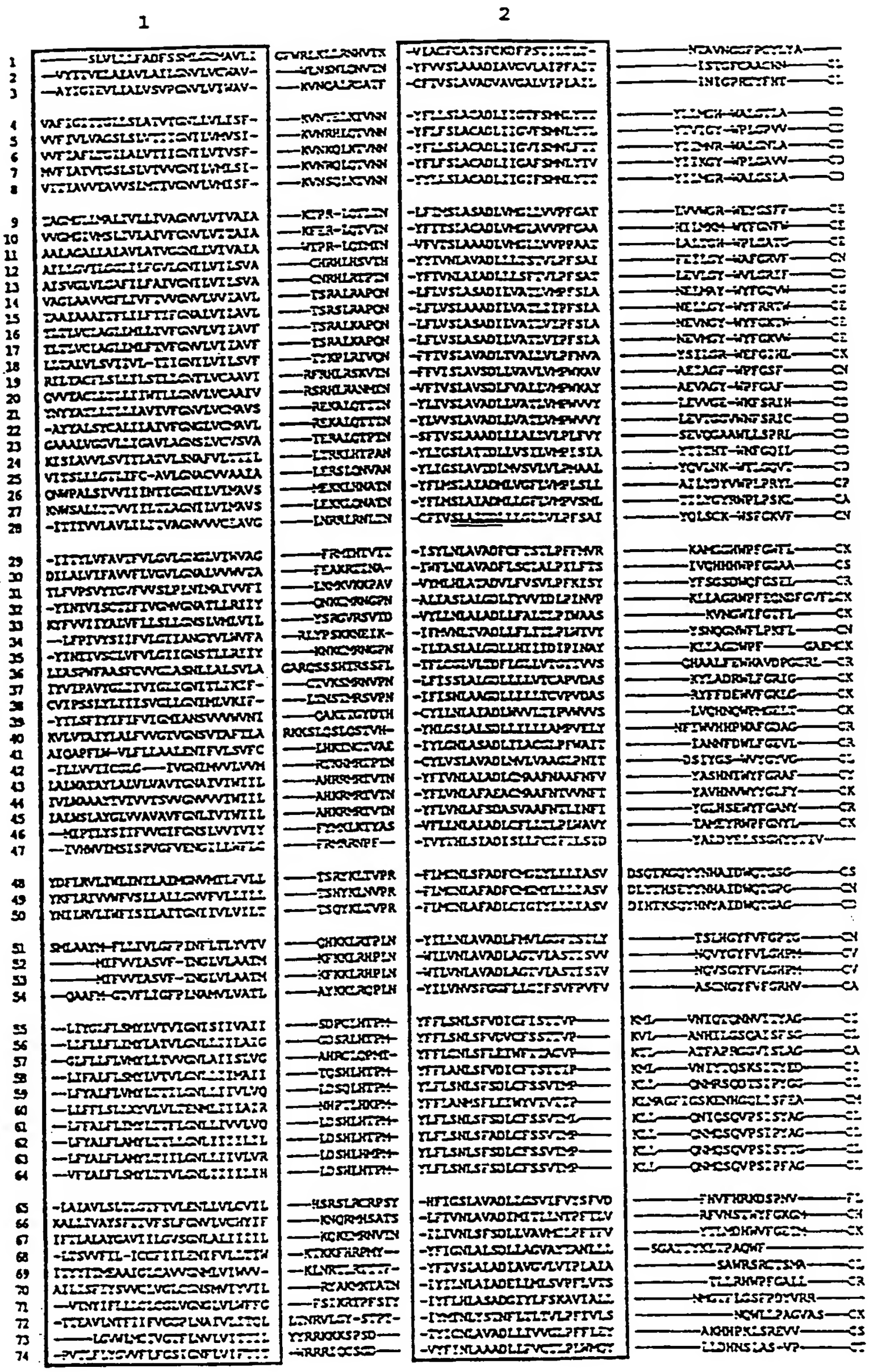

FIGURE 8C

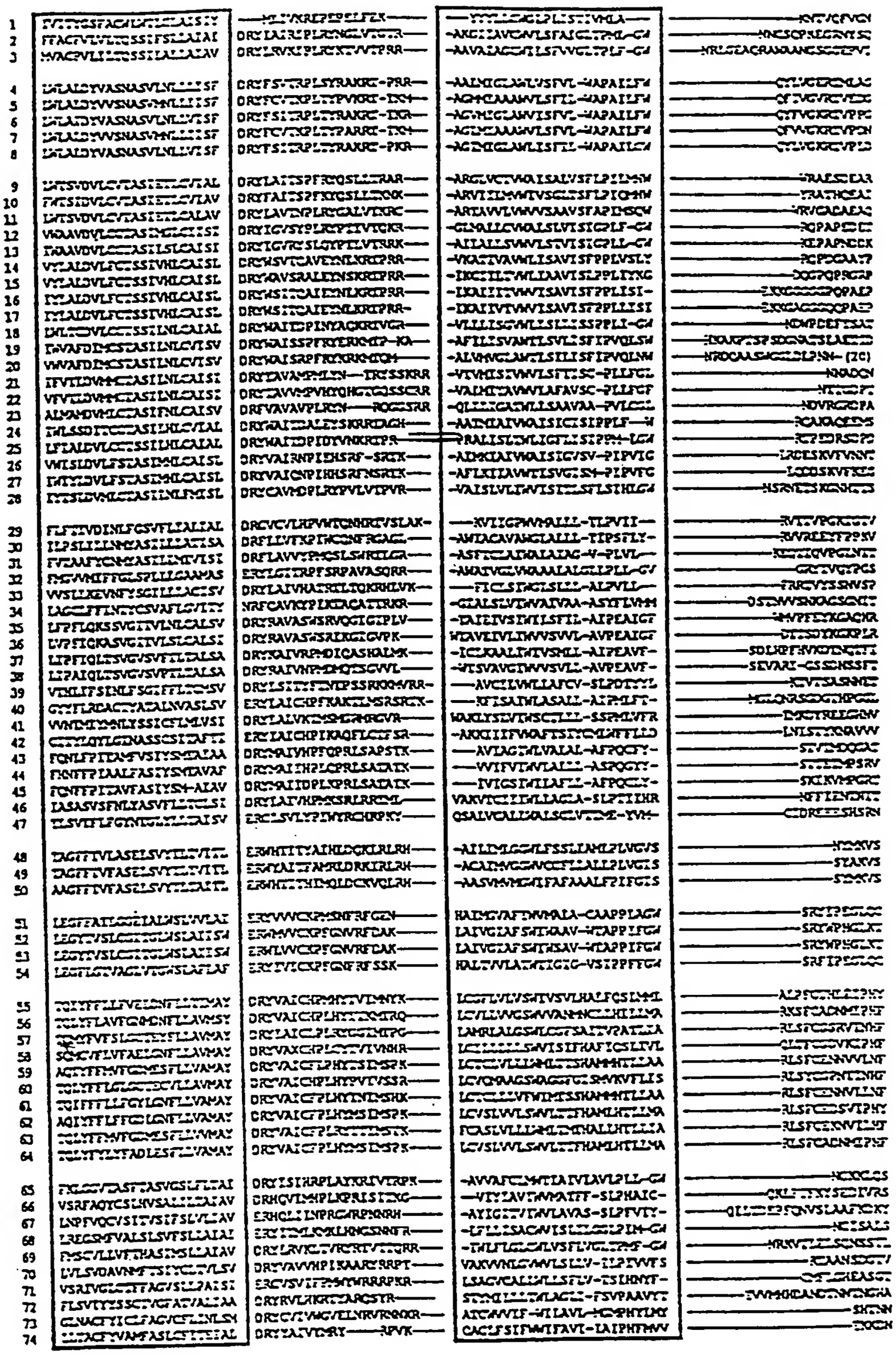

FIGURE 8D

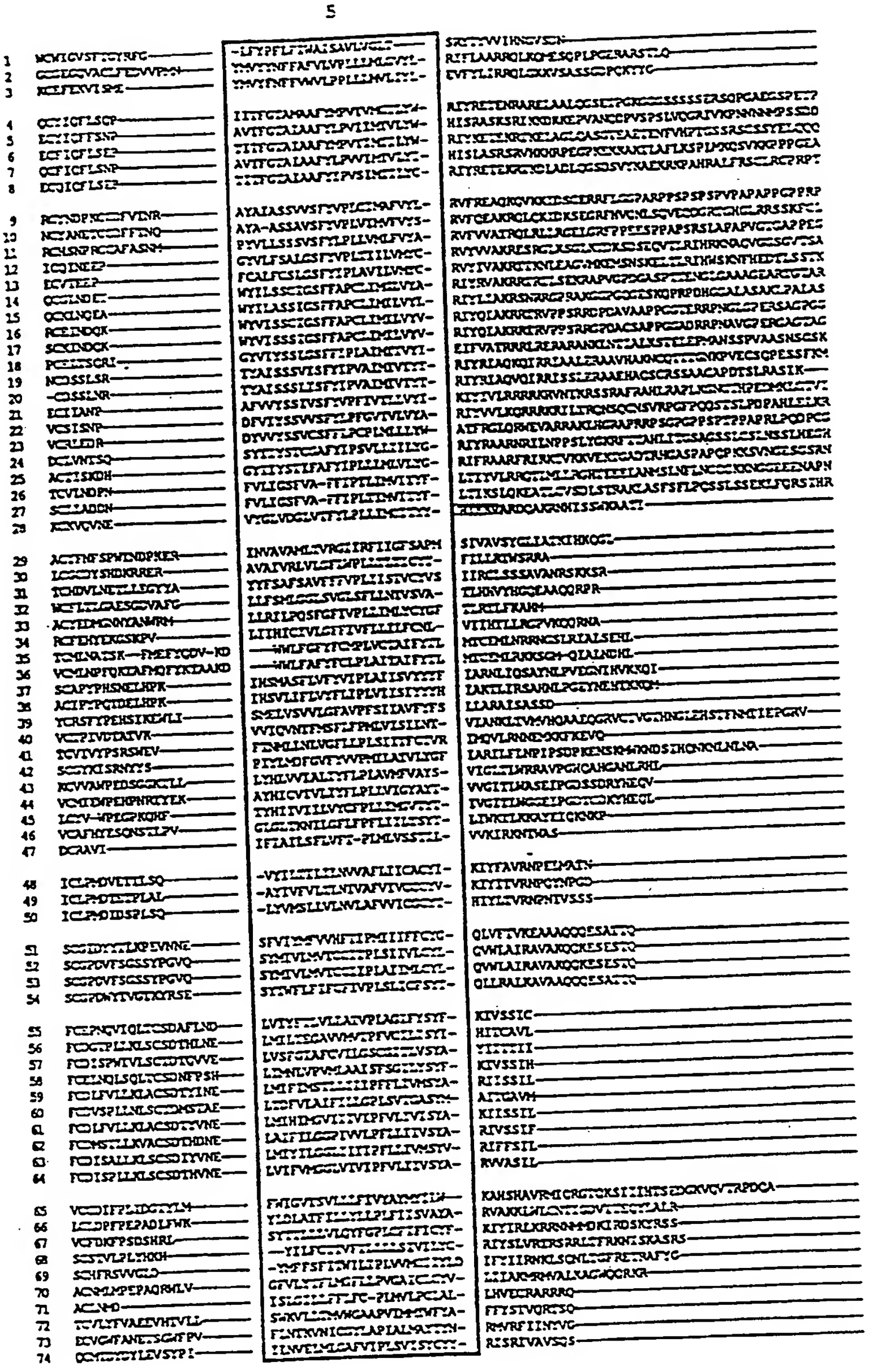

FIGURE 8E

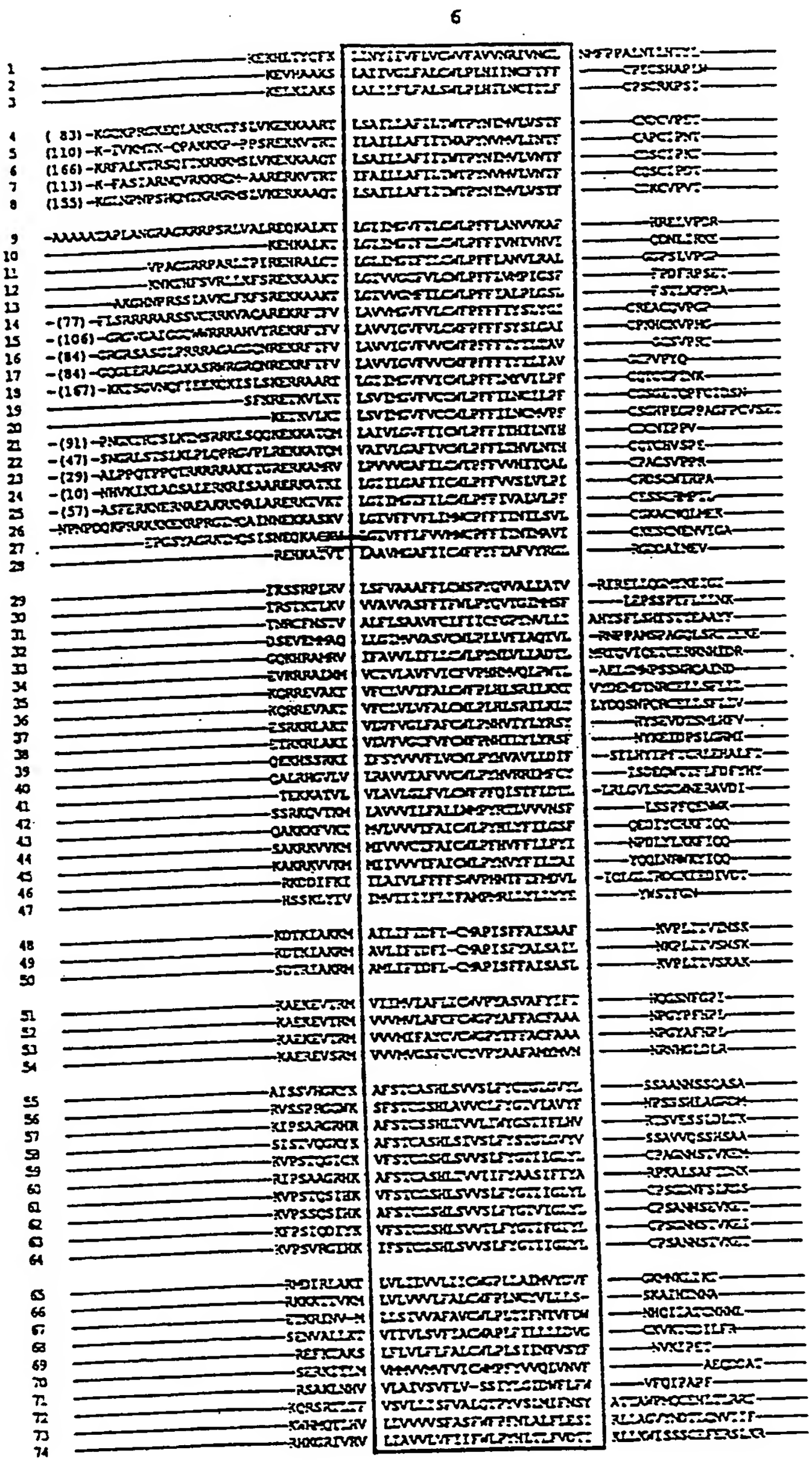

FIGURE 8F

7

FIGURE 8G

INTERNATIONAL SEARCH REPORT

Int. ..ional application No.
PCT/US93/08528

A. CLASSIFICATION OF SUBJECT MATTER

IPC(5) :C07K 7/00, 15/06; C12N 15/12
US CL :435/69.1; 514/12, 13, 14, 15, 16, 17; 530/387.9
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 435/69.1; 514/12, 13, 14, 15, 16, 17; 530/387.9

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

APS, STN/MEDLINE
search terms: G protein coupled, receptor#, fragment#

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	NATURE, Vol. 336, issued 22 December 1988, J. R. Bunzow et.al.,"Cloning and expression of a rat D2 dopamine receptor cDNA", pages 783-787. See entire document.	1-41
A	Biochemistry, Vol. 26, No. 10, issued 19 May 1987, H. G. Dohlman et.al.,"A Family of Receptors Coupled to Guanine Nucleotide Regulatory Proteins", pages 2657-2664. See entire document.	1-41
A	BIO/TECHNOLOGY, Vol. 7, issued September 1989, S. Marullo et.al.,"EXPRESSION OF HUMAN ß1 AND ß2 ADRENERGIC RECEPTORS IN *E. COLI* AS A NEW TOOL FOR LIGAND SCREENING", pages 923-927. See entire document.	1-41

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

* Special categories of cited documents:
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"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
25 October 1993	DEC 02 1993
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. NOT APPLICABLE	Authorized officer JOHN D. ULM Telephone No. (703) 308-0196

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